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SENSORY CORTEX OF CHIMPANZEE*

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(Received for publication June 26, 1940)

INTRODUCTION

RECENTLY two of the present authors (12) gave a preliminary report on the location, extent and subdivision of the sensory cortex of the chimpanzee based on experiments on four animals. We can now present the results of new experiments on five more chimpanzees. The technique used was essentially the same as that of the experiments of the preliminary paper, namely local strychninization of the cerebral cortex in the fully anesthetized animal and investigation of the distribution of the "strychnine spikes" appearing in the electrocorticograms (ECGs) of various portions of the cerebral cortex. The only difference is that in these new experiments thirty-six electrodes were placed on the cortex instead of six as in the previous experiments. Obviously this resulted in much more detailed information. What needs elucidation is how the location, extent and functional organization of the "sensory" cortex can be determined in experiments such as these, in the fully anesthetized animal.

For more than thirty years the use of local strychninization of the central nervous system (CNS) has proved itself an almost ideal method for the study of the location and functional organization of sensory systems in the CNS. In 1909–1913 the senior author (5) applied this method to the spinal cord. In 1915 he (6) found that local strychninization *within* a certain region of the cerebral cortex of the cat, after recovery of the animal from the operative anesthesia, results in transient—for about 30 minutes—typical symptoms of sensory excitation: paraesthesiae and hypersensitivity of the skin and deeper structures. Strychninization *without* this region did not result in sensory disturbances. In 1923 the same author (7) using the same methods, namely local strychninization in conjunction with "clinical" observations of the animal, delimited the sensory cortex of the macaque monkey. The obvious conclusion from these two series of experiments is that the region thus delimited subserves somatic sensory functions, is the "sensory" cortex.

After the "sensory" nuclei of the thalamus opticus of the cat had been diagnosed by the same physiological methods (14), Dusser de Barenne and McCulloch (10) showed that local strychninization of the sensory cortex, as ascertained by the first combination of methods, results—even in the fully anesthetized animal—in activation of these very same thalamic nuclei:

* Aided by a grant from the John and Mary R. Markle Foundation.

† On leave of absence from the Department of Neurology and Neurosurgery, University of Illinois.

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local strychninization of the various subdivisions of the "sensory" cortex results in the appearance of large and rapid voltage fluctuations—"strychnine spikes"—in the electrograms of the corresponding "sensory" nuclei of the thalamus.

Finally Dusser de Barenne and McCulloch (9) and these authors with Ogawa (13) studied the distribution of the strychnine spikes in the electrograms of the cerebral cortex following its local strychninization in the fully anesthetized monkey. Again the same region was as delimited with the original combination of methods. Local strychninization *within* this region resulted in widespread strychnine spikes with a typical distribution following strychninization of each constituent area; strychninization *without* this region never resulted in the appearance of strychnine spikes in the electrograms taken within the region. Furthermore, the distribution of the strychnine spikes is specific for each constituent area of this region. The obvious conclusion from these various pieces of experimental evidence is that the distribution of the strychnine spikes in the cerebral cortex following its local strychninization permits one to determine the location, extent and functional organization of the "sensory" cortex even in the fully anesthetized animal.

"Clinical" observation of as strong an animal as the anthropoid ape after local strychninization of its cerebral cortex would be too dangerous for the experimenter. We have, therefore, for the study of the chimpanzee's sensory cortex, employed the combination of methods which can be used in the fully anesthetized animal. Again this combination of methods has revealed on the surface of the hemisphere a very large region, the location, extent and functional organization of which is comparable to that of the sensory cortex of the macaque monkey. The obvious inference again is *that the region so disclosed is the sensory cortex of the chimpanzee.*

On all hemispheres of this new series, except one, extensive electrical stimulations of the cortex were performed with special stimulators (see the section on methods) allowing the use of various pulseforms. The relevant findings of these stimulation experiments and their correlation with the findings in this paper will be published in a separate paper.

METHODS

These experiments were performed on 5 immature, 2.5 to 3.5 years old, chimpanzees (*Pan satyrus*), fully anesthetized with Dial* (0.35 −0.45 cc. per kg. body weight, half of the doses given intraperitoneally, half intramuscularly). When the animal was fully under narcosis the head was clamped in a special head holder, and the body placed on an inclined board so that the head was lower than the hindquarters of the animal; this was done to maintain proper cerebral circulation.

Each investigation on one animal lasted from 3 to 3.5 days without interruption. It was, therefore, necessary to work in day- and nightshifts, usually from 12:00 noon until 12:00 midnight and from 12:00 a.m. until 12:00 p.m.† During the first 1.5 to 2 days the

* We wish to thank the Ciba Co. for kindly putting the Dial at our disposal.

† We wish to extend our thanks to Messrs. Willard B. Chamberlain, Craig W. Goodwin, John M. Hamilton and Arthur A. Ward for their unremittingly enthusiastic assistance in these long and weary experiments.

sensory cortex of one hemisphere was investigated, the rest of the time was devoted to the exploration of the second hemisphere.

After exposure of the larger part of the convexity of one hemisphere several photographs of the exposed region were taken from different angles to get as little perspective distortion as possible in the final composite drawing of the hemisphere. Lifesize prints were made to record accurately the location and extent of the several local strychninizations and of the electrically excitable "motor" cortex.

The investigation of each hemisphere was begun with a careful exploration of the "motor" cortex. For this a specially constructed stimulator designed and built by Mr. Craig W. Goodwin, the electronic engineer of this laboratory, was used.* This apparatus allows independent variation of the rising and falling phases of each individual pulse and the frequency of the pulses per second, the pattern-frequency of the stimulation, within a wide range, and the number of pulses per stimulation. For several years Dusser de Barenne and McCulloch had known (from unpublished experiments) that with long pulses —of several sigmas' duration—the voltage required to stimulate the "motor" cortex is much lower than with short pulses and that especially the duration of the descending phase seems significant; under moderate Dial-anesthesia a descending phase of from 8 to 12σ duration is optimum. Where necessary, due caution was taken in regard to the disturbing influence of facilitation and extinction (8). In other instances facilitation was used as a useful factor in determining the most frontal boundary of the "motor" cortex. An important feature of the stimulatory exploration was also the delimitation of the boundaries between the leg-, arm- and face-subdivisions of the "motor" cortex. For further details see the next paper on the "motor" cortex of the chimpanzee.

After the careful exploration and mapping of the "motor" cortex the experiments with local strychninization were begun. Because of the tremendous functional complexity of the chimpanzee's cortex it was decided to concentrate our efforts in this group of animals mostly on the arm-subdivision; in the last chimpanzee attention was focussed predominantly on the leg-subdivision. Six columns of 6 stigmatic Ag-$AgCl_2$ electrodes were placed on the exposed portion of the cortex, the uppermost of each column high up in the leg-subdivision, dorsal to the boundary between the leg- and arm-subdivisions; the 5 others of each column were spread vertically over the dorso-ventral extent of the arm-subdivision. In several of the experiments the most ventral electrode of each column was placed in the face-subdivision. Thus, although in these experiments most information was obtained about the arm region of the sensory cortex, a good deal of evidence about the leg- and face-regions and the functional boundaries between the three major subdivisions of the sensory cortex was also acquired. On the precentral cortex the results of the electrical explorations gave useful information for the placement of the electrodes; on nearly all of the postcentral cortex this guiding factor was not available and we relied on experience with the functional boundaries obtained in the chimpanzees of the preliminary paper.

The wires from all 36 electrodes were connected to a 6 pole—6 throw switch and from this to the 5 amplifier sets of 5 Grass inkwriter-oscillographs in such a way that in one position of the switch all 6 electrodes of one column were connected to the oscillographs. Thus, by turning the switch, each column of electrodes on the cortex could quickly be connected with the amplifiers and oscillographs. If we call the 6 electrodes in each column from above downwards, a, b, c, d, e and f and the 5 oscillograph channels A, B, C, D and E, the hook-up was such that electrodes a and b were connected to channel A, electrodes b and c to channel B . . . , electrodes e and f to channel E. A change or disturbance of the electrical activity in the cortex under or near electrode a will affect only channel A, stimultaneous and inverted strychnine spikes or any other change in the ECGs in channels A and B signifies a disturbance under or near electrode b, simultaneous changes in channels C and D a disturbance under or near electrode d . . . and a change in the ECG of channel E by itself a disturbance under electrode f. Thus each change in the ECGs of any channel or group of channels reflects a change in the activity of the cortex under or near a particular electrode or group of electrodes. Thus, in turning the 6 pole—6 throw switch one can investigate in quick selection and succession the ECGs of the cortex under or near the 6 electrodes of each of the 6 columns.

The taking of the ECGs before and after each strychninization constitutes one experiment, whose actual course usually was as follows: (i) the taking as "control runs" for 1 min. of the "normal" ECGs for each of the 6 columns of electrodes, (ii) the local strych-

* Mr. Goodwin will describe this stimulator separately in the near future.

ninization of the cortex by applying a small piece of filterpaper of appropriate size and shape soaked in a 3 per cent solution of strychnine sulfate colored with toluidine blue; (iii) the taking of half-minute runs of ECGs for each of the 6 columns of electrodes in succession until any change, if such resulted from the strychninization, had passed off. Five to ten minutes after its application the filterpaper was removed and any fluid at the site of strychninization carefully blotted. Usually after 25 to 45 minutes the effects of such a strychninization had passed off, depending upon the depth of narcosis, the circulation, etc.

In our work on the macaque's cortex truly local strychninizations were always performed, *i.e.*, strychnine-filter papers of a few square millimeters applied. In the chimpanzee the effects of such local strychninizations are very much more restricted than in the

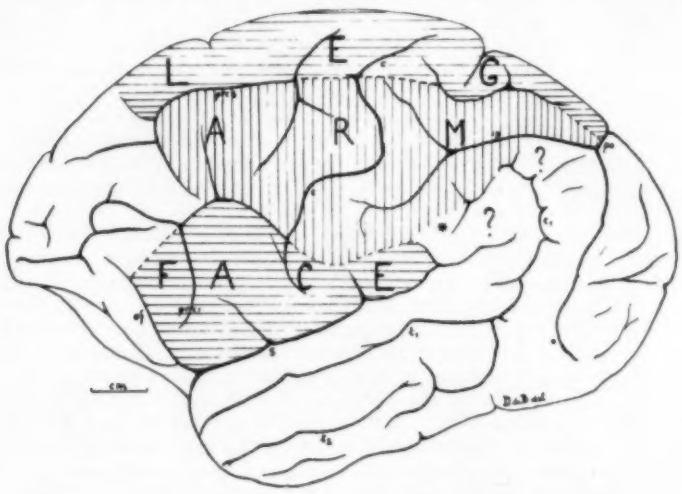

FIG. 1. Sensory cortex of the chimpanzee. This figure represents as accurately as is possible in one plane the outer surface of one hemisphere of chimpanzee No. 4. The precentral boundary between the face- and arm-subdivisions lies in this hemisphere unusually low, but was verified both by electrical stimulation with motor response and with the strychnine method. It is also unusual that this boundary is marked by a definite sulcus across the precentral gyrus. The figure schematizes the results of over 200 observations on this one brain.

macaque; therefore, the strychnine filterpapers used in the chimpanzee experiments were taken larger, 3×5 or 2×10 millimeters.

Thus, in general, during each experiment from 8 to 14 series of ECGs from the 6 columns of electrodes were taken. Usually between 15 to 25 strychninizations were performed on one hemisphere, *i.e.*, 30 to 50 experiments performed on the brain of each chimpanzee.

At the end of such an investigation, lasting without interruption for 3 to 4 days, the brain was injected through the carotids with 15 per cent neutral formalin, then removed from the skull and placed in formalin. After 12 to 24 hours the brain was weighed and carefully measured. After a few days the soft membranes were peeled off and the brain photographed before and after removal of the brainstem and cerebellum and after splitting in the midplane. Finally all the strychninizations were carefully mapped on life size photographs of the hemispheres.

Then the analysis of the several thousand feet of record was begun and the change of the ECG under each electrode in each experiment marked on drawings (twice life size) of each hemisphere ("firing," suppression, "spindles," increase of activity, no change). Thus the final plotting of the results of each experiment on the cortex of one hemisphere is based on the study of circa 400 ECGs (each comprising 8 or more records) and the final composite diagram, on that of well over 100,000 records.

Results

Location, extent and subdivision of sensory cortex

The experiments of this new series have essentially confirmed the location and extent of the sensory cortex of the chimpanzee as given in the preliminary report and as reproduced in Fig. 1. They have permitted us to answer a few of the questions left in this diagram. Those small areas marked there with a ? do not belong, as we can definitely state now, to the sensory cortex.

We are also in a position now to state that the small triangular area

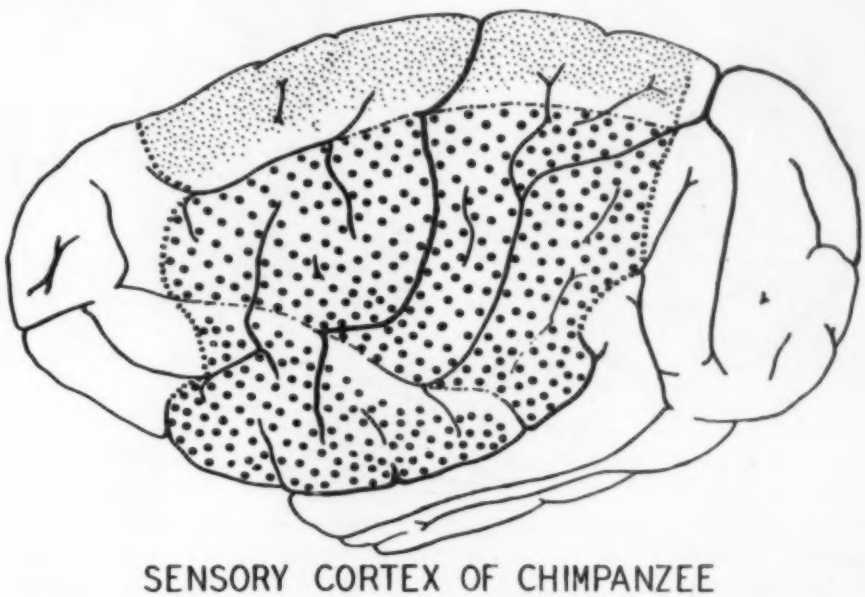

FIG. 2. A composite drawing showing the extent and location of the sensory cortex and its subdivisions for leg (⁂), arm (⁂) and face (⁂). The regions for trunk (between arm and leg) and for neck (between arm and face) are left blank.
× × × = anterior and posterior margins of the sensory cortex; — • — • = boundaries of arm-subdivision.

marked with an * in the first diagram belongs to the arm-subdivision. The posterior border of the sensory leg cortex did not extend in the last 5 animals all the way to the fissura parieto-occipitalis externa (ope), as was the case in the fourth animal of the first series; apparently individual variations are not infrequent.

In Fig. 2 is given an "average" (see discussion) aspect of the convexity of the chimpanzee's brain; in it are indicated also the location, extent and subdivision of the sensory cortex as delimited in these new experiments. It will be seen that this cortex occupies a large portion of the hemisphere on its outer surface both before and behind the fissura centralis and comprises three major subdivisions: the leg-, arm- and face-subdivisions. Between the

leg- and arm-subdivisions lies a narrow strip of cortex in which presumably the trunk is represented sensorially. This statement is based on (i.) the existence in the precentral cortex of an intermediate "motor" trunk region and (ii.) the occurrence of small or questionable strychnine spikes within both the pre- and postcentral portion of this intermediate region from strychninizations definitely in the leg- or arm-subdivision. Between the arm- and face-subdivisions lies a narrow strip of cortex in which presumably the neck is

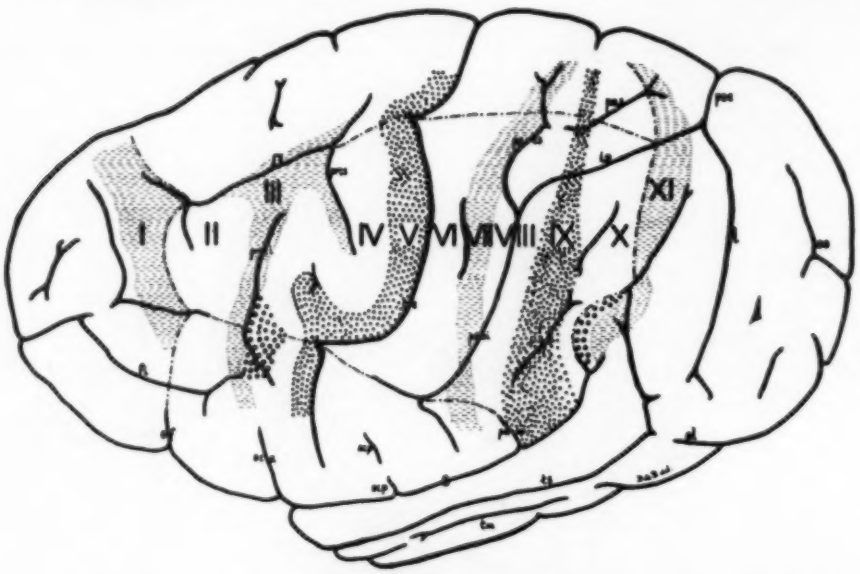

FIG. 3. The extent, location and functional subdivisions of the sensory arm cortex into physiologically distinguishable bands, Nos. II–X, and of the immediately adjacent bands, Nos. I and XI, indicated on a composite drawing representing the arm area in the center of the field. The bands giving suppression, Nos. I, III, VII and XI, are marked thus: ☰☰☰. Small ⁘ indicate bands V and IX. Large ⁘ mark the "dud" areas. Areas between trunk and arm and between arm and neck are marked —•—•.

represented sensorially. The reasons for this statement are the same as for the trunk region, mutatis mutandis.

While we refer to this region as the "neck" region it should be remembered that in these experiments the head of the animal was fixed, so that the only musculature about whose contraction definite observations could be made was the superficial neck musculature: platysma, sterno-cleido, splenius capitis, pinna muscles, etc. The boundaries of these two intermediate regions are drawn in Fig. 2 as more distinct towards the arm-subdivision because we have enough information to establish these margins fairly accurately.

Functional organization of sensory cortex

In the previous work on the macaque's sensory cortex it was found that the distribution of the strychnine spikes following local strychninization of

some area is not only beyond the limits of this area but follows a definite "pattern" for each area. This means, as has been established by further investigations (11), that the various areas of the sensory cortex of the macaque monkey have different interareal neuronal connections. Thus this combination of methods reveals what we have called the "functional organization" of the macaque's sensory cortex

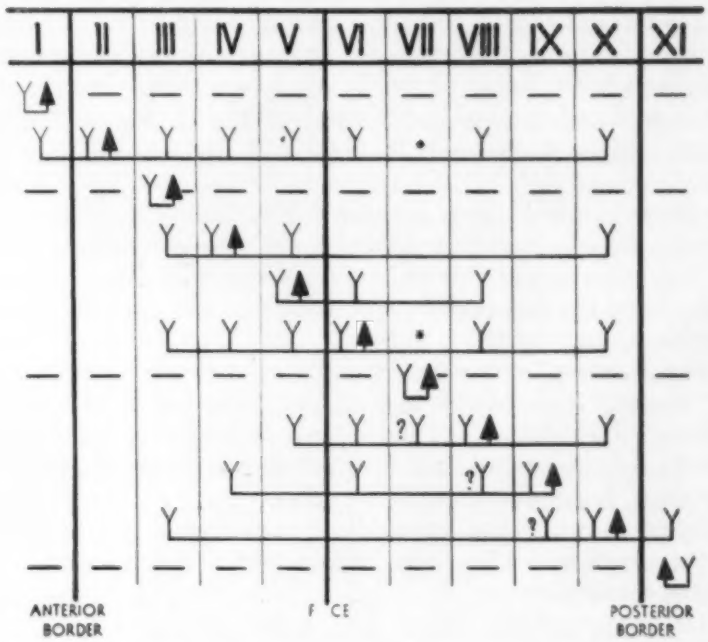

FIG. 4. In Figure 4 are represented diagrammatically the directed functional (and anatomical) relations between the various cortical bands of the arm-subdivision of the sensory cortex found in these experiments and also those of bands I and XI adjacent to but outside of the sensory cortex. Anterior and posterior borders are the limits of the sensory cortex. The suppression of the ECG of various bands upon strychninization of bands I, III, VII and XI is indicated thus: ———.

F CE = fissura centralis; * = no certain evidence; ?Y = definite "firing" but uncertainty whether strychnine invaded region so "fired."

The same is true for this cortex of the chimpanzee, but with differences: (i) with truly local strychninization the distribution of the strychnine spikes is in this animal much less widespread than in the macaque, sometimes confined to a relatively small region in the neighborhood of the site of strychninization; (ii) when the spikes are present in another more or less remote region, only a small portion of that region is involved.

Concentrating attention on the arm-subdivision it was found to be composed of several functionally dissimilar vertical "bands" of cortex, characterized by: (i) the unique distribution of the strychnine spikes following strychninization within any one band; (ii) the appearance of strychnine spikes within it following strychninization of other bands.

Unfortunately the only complete cytoarchitectonic map of the chimpanzee's cortex is that of Campbell (3), which fails to show many differentiations found functionally in these experiments. Furthermore, the other available cytoarchitectonic studies on the precentral areas 4 and 6 of the chimpanzee (Brodmann, 1, Bucy, 2) differ so widely from Campbell's findings, as to be of little help here. We have, therefore, abstained from any attempt to correlate anatomy and physiology here and constructed our diagram so as to indicate only the physiological differentiation met in our experiments. We have, therefore, assigned to each functionally unique band so revealed an arbitrary number, I through XI. Bands II through X comprise the sensory arm region, whereas bands I and XI (see below) lie without it. Figure 3 presents the location and extent of these bands, mainly in the arm-subdivision, on the chimpanzee's brain.

While these bands indicate greater differentiation in the chimpanzee's sensory cortex than in the macaque's, there appear certain similarities to the functional organization of this animal's sensory cortex as indicated below. Figure 4 presents the functional organization of the arm-subdivision of the chimpanzee's sensory cortex.

The most anterior band of the chimpanzee's sensory cortex, No. II, like area 6 of the macaque, shows the widest distribution of the strychnine spikes, "firing" practically all of the sensory arm cortex except band IX and being fired by no other band than itself. It should be noted that, like area 6 of the macaque, local strychninization of arm band II "fires" not only the arm-subdivision but also the leg-subdivision and even the face-subdivision. It should further be noted that strychninization of band II also "fires" band I, outside the sensory cortex.

Band III has properties comparable to those of area 4-s in the macaque, in that it gives pure "suppression" of electrical activity of other regions of the sensory cortex and spikes only itself.

Bands IV and V together "behave" functionally like area 4 of the macaque. Local strychninization of band VI results in widespread strychnine spikes in both the pre- and postcentral arm cortex; it does not "fire" band II, or band IX.

Band VII is again a suppressor region comparable to the postcentral suppressor area in the macaque's brain and spikes only itself.

Bands VIII, IX and X together resemble the sensory cortex of the macaque's cortex behind its postcentral suppressor area. Whereas local strychninization of bands VIII and IX respect functional boundaries, this is not the case with band X. Local strychninization of leg X "fires" not only itself but also arm X and leg and arm III, local strychninization of arm X "fires" not not only itself but also leg X and leg and arm III.

These are the essential functional similarities of the sensory cortices of chimpanzee and macaque; now as to the dissimilarities.

The outstanding difference is that whereas in the macaque when spiking occurs in an area of the sensory cortex it generally involves all parts of this

area, even though the strychninization is truly local, the spiking upon strychninization within a band of the chimpanzee's cortex is much more restricted even when the area strychninized is much larger. Even with 36 electrodes on the cortex and relatively large strychninizations one cannot hope to obtain the complete distribution of strychnine spikes from a given area in any single experiment. This is not and cannot be represented in Fig. 3 and 4, which are composites of all strychninizations in all 6 animals and show the greatest distribution obtained. What does appear in these figures is the greater differentiation into more bands than areas that could be distinguished in the macaque's sensory arm region, witness the differentiation of the immediate precentral cortex in the chimpanzee, subdivided into bands V and IV, (together comparable to area 4 of the macaque) and the far postcentral bands VIII, IX and X. Characteristic of the chimpanzee's sensory cortex is the finding of "firing" of remote regions without "firing" of some intermediate region or regions: the failure of bands II and VI to "fire" band IX, though both "fire" band X; the failure of band IV to "fire" bands VI, VII, VIII, and IX, though it "fires" band X; the failure of band V to "fire" VII, though it "fires" VIII; the failure of band VIII to "fire" band IX, though it "fires" band X; the failure of band IX to "fire" bands V and VII, though it "fires" bands VI and IV, and finally the failure of band X to "fire" bands VIII, VII, VI, V and IV, though it "fires" band III.

An interesting finding is that in the precentral sensory cortex (see Fig. 3) lies a "dud" area, "dud" in this sense, that its strychninization "fires" no other area and that it is "fired" by strychninization of no other area. Above the end of the fissura Sylvii, bulging into the sensory cortex, but not part of it, lies a second "dud" area in the same sense as the first area (see Fig. 3).

Anterior and posterior to the sensory arm cortex were found two bands, I and XI respectively, the local strychninization of which results in a marked suppression of the electrical activity of a great part of the convexity of the hemisphere. Local strychninization of band I results not only in suppression of the electrical activity of the whole arm cortex, but also of that of the leg-, trunk-, neck- and face-subdivisions and of that of band XI; local strychninization of band XI similarly gives suppression of the electrical activity of the entire sensory cortex and of that of band I. It is interesting to note that this widespread suppression from these two areas does not occur simultaneously in all bands of the sensory cortex, but slowly, in the course of many minutes, sweeps across this cortex in a definite sequence, the bands nearest to that strychninized "going under" first, those more remote later. (See Fig. 5 and 6)

Figure 6 gives the right hemisphere of chimpanzee VI on which this particular experiment was performed to obtain the records of Fig. 5 and the position of the electrodes with the changes of the electrical activity of the cortex underneath each of these electrodes (+ for "firing," − for suppression, 0 for no change), and the site and extent of the strychninization.

Very interesting is the finding that the sequence of the bands is more orderly

COLUMNS OF ELECTRODES

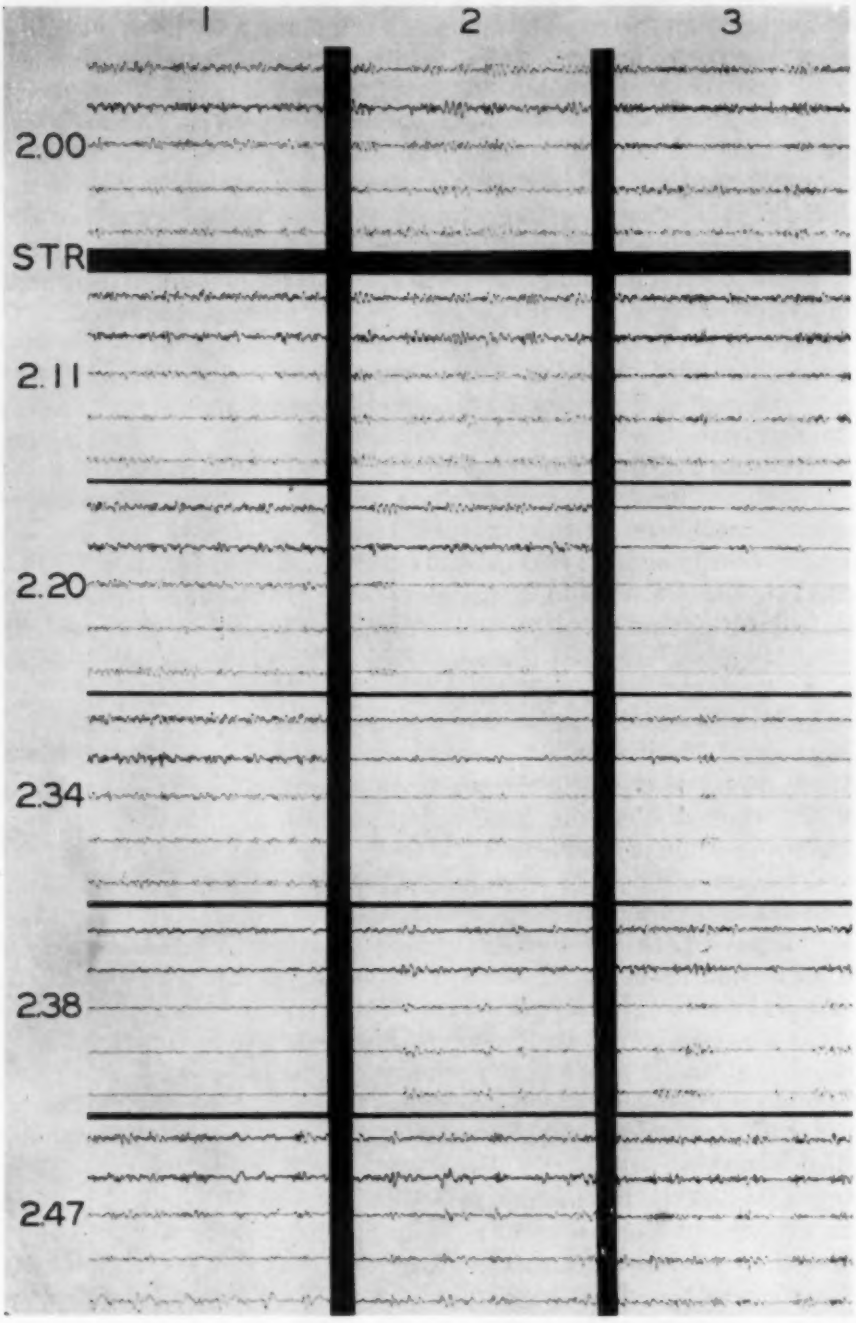

FIG. 5. Nov. 7, 1939. Chimpanzee VI. Right hemisphere. Second day. Strychninization No. 18 at S in band XI (see Fig. 6) at 2:04 p.m. between the recording of the ECGs of rows 1 and 2. (For arrangement of electrodes on cortex and on records and their connections with amplifier oscillograph sets see Fig. 6.) Note the "'firing" in the ECGs coresponding to electrodes b, c,d and e of column 6, and the "sweep" of the suppression of the electrical activity across the cortex.

COLUMNS OF ELECTRODES

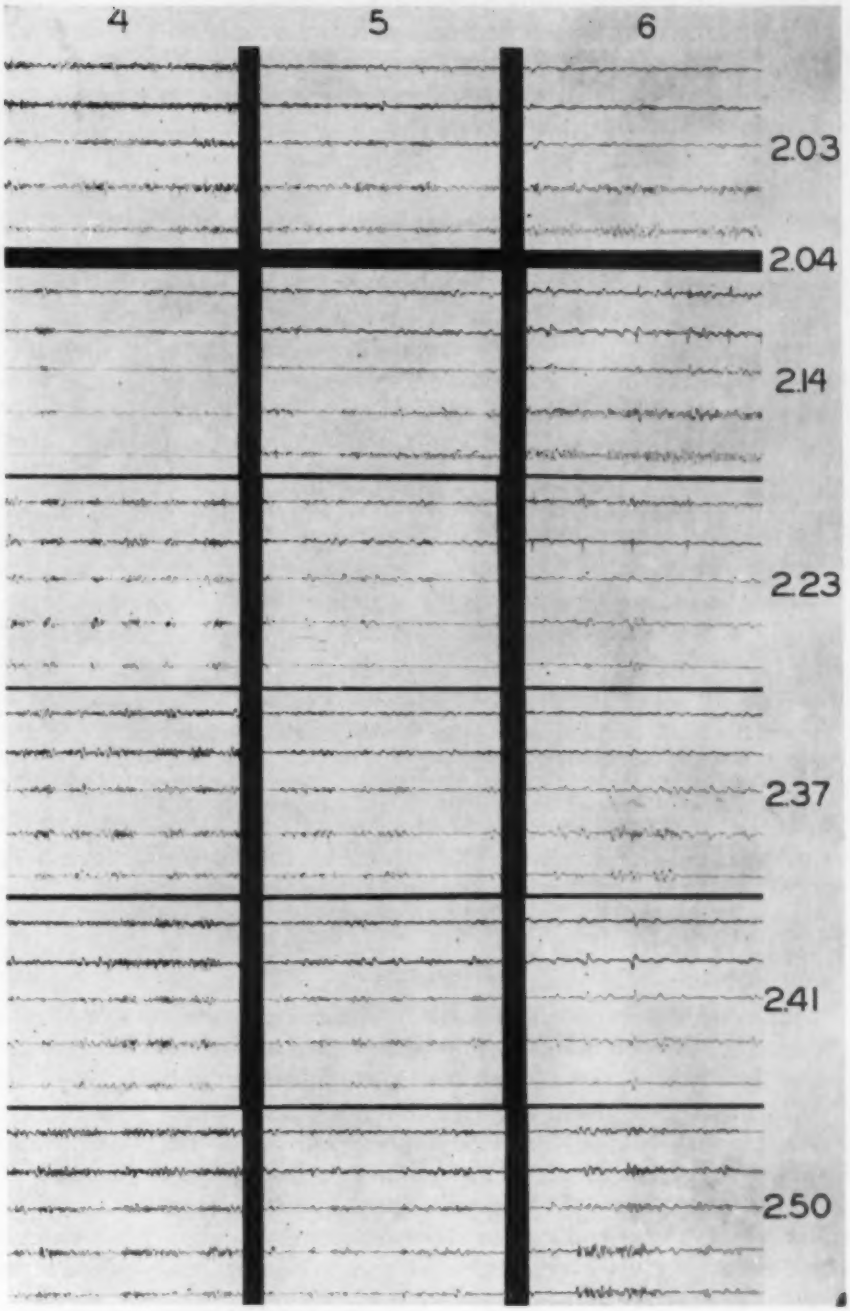

FIG. 5. Nov. 7, 1939. Chimpanzee VI. Right hemisphere. Second day. Strychninization No. 18 in band XI (at S in Fig. 6 and indicated by STR in Fig. 5) at 2:04 p.m. between the recording of the ECGs of rows 1 and 2. (For arrangement of electrodes on cortex and on records and their connections with amplifier-oscillograph sets see Fig. 6.) Note the "firing" in the ECGs corresponding to electrodes b, c, d and e of column 6, and the "sweep" of the suppression of the electrical activity across the cortex.

than that of the sulci, *i.e.*, on crossing a sulcus a band may appear interrupted and one of its portions appear displaced anteriorly or posteriorly depending upon the angle between the band and the sulcus on the surface. For instance, if in a particular brain the "spur" of the first temporal sulcus bends anteriorly, the portion of band XI above this spur lies anterior to its continuation below the spur, whereas in an animal in which the spur of the first temporal sulcus bends posteriorly, the superior portion of band XI lies

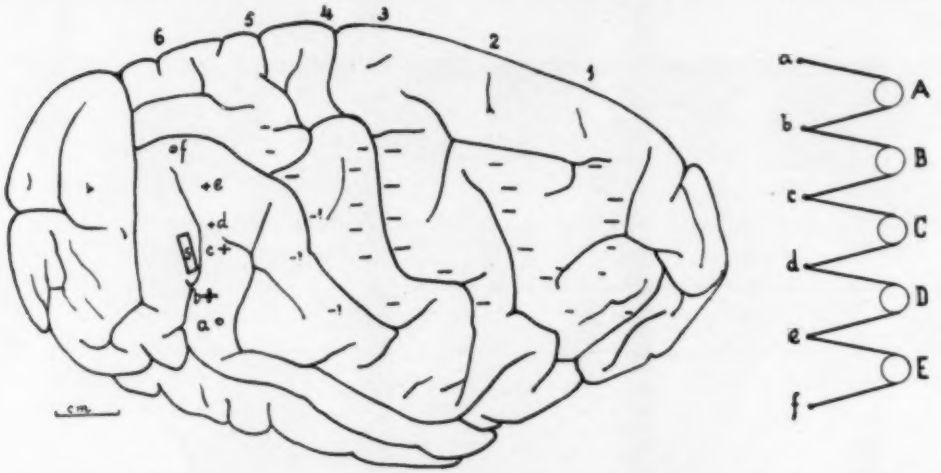

FIG. 6. Right hemisphere of chimpanzee VI with location and extent of strychninization (S), positions and arrangement of the 6 columns of 6 electrodes and the change in electrical activity under each electrode (+for "firing," − for suppression, 0 for no change). This figure refers to the experiment recorded in Fig. 5. Notice that the arrangement of electrodes on cortex and in records is inverted. a, b, c, d, e and f represent the 6 electrodes of any column, A, B, C, D and E the 5 amplifier-oscillograph sets.

posterior to its inferior, or ventral, portion. This finding must mean that the location of the bands is more fundamental than the location and configuration of the sulci crossed by the bands.

DISCUSSION

The most salient point which these new investigations have brought out, just because of the great amount of information obtained in each hemisphere, is that it is almost impossible to compose a reliable diagram of the location, extent, subdivision and functional organization of "*the*" chimpanzee's sensory cortex. The variability in the configuration of this animal's cortex is so great as to preclude any definite homologization of any but the principal fissures and sulci. The size, shape, position and direction of the secondary sulci is so variable that these (sometimes, even) often, cannot be identified with certainty. Nevertheless it was necessary to use some composite diagram of the external configuration of the hemisphere. After a careful study not only of the hemispheres in our own collection but also of the available material in the literature (Retzius, Mingazzini and others) the

composite diagram presented in Fig. 2 and 3 was made. This is believed to represent not too unfaithfully the "average" external aspect of the chimpanzee's brain. Since in nearly all of these studies attention was focussed on the arm-subdivision, this diagram was composed from photographs centered upon the middle of this subdivision. Given the great variability of the external configuration of the chimpanzee's hemisphere it will be readily understood that the sites of individual strychninizations and electrodes are extremely difficult to homologize from hemisphere to hemisphere. Although these sites were in each instance plotted on photographs and drawings of that hemisphere on which the particular experiment was performed, it was found most practicable for the final synopsis to transfer them to sites homologized as well as possible on the composite diagram.

The difficulties mentioned are especially great with respect to band VII because it is narrow and occupies the posterior margin of the extremely variable postcentral gyrus. When this gyrus is wide and has a longitudinal sulcus on its convexity band VII is found as indicated in Fig. 3; when the gyrus is narrow it is sometimes impossible to find band VII in the central position of the arm-subdivision and, if found, it may appear immediately behind the postcentral sulcus. Most difficult are those hemispheres in which the postcentral gyrus is narrow and the junction of the superior postcentral sulcus with the intraparietal sulcus is low down, far forward and complicated in form while the longitudinal dimple on the postcentral gyrus is absent or at least does not appear as a separate sulcus. This variability is so great as to make it almost impossible to place electrodes wilfully in this particular band. The diagram of functional organization (Fig. 4) shows, therefore, the most probable changes in activity following the various strychninizations with electrodes probably placed in band VII. The asterisks indicate complete uncertainty in this respect. In chimpanzee 9 we have evidence that if electrodes are placed in the leg region of band VII, strychninization of band II and of band VI "fires" band VII. We are, therefore, inclined to believe that the same is true of the arm-subdivision, where evidence is still to seek.

Similar difficulties arise especially for the more dorsal part of band IX, where it narrows down as it passes into the trunk region, and the variability of the ends of the inferior parietal sulcus, the fissura Sylvii and the first temporal sulcus complicates the picture. However, in the case of band IX enough experimental evidence (sites of electrodes and strychninizations) was available to overcome, in our opinion, the difficulties.

The question marks in Fig. 4 do not indicate uncertainty as to "firing" or position of the electrodes in these bands, but signify that the strychnine may have extended into the region so fired from that adjacent region to which it was applied. In each case the firing marked with a ? was only in the proximity of the strychninization and did not involve more remote parts of the band under consideration.

Not indicated in Fig. 4 are: that in chimpanzee 9 strychninization of

band XI in the leg region, besides "firing" itself, suppressed itself, and that in one instance strychninization in band I, besides "firing" this band, questionably suppressed the same. We shall now discuss the bands seriatim.

Band I. This band lies outside the sensory cortex by the criterion that strychninization within it never "fires" any portion of the sensory cortex. Its primary characteristic is that its strychninization gives suppression of cortical electrical activity, which may involve the entire sensory cortex and even extend beyond it. This suppression does not respect functional boundaries between the major subdivisions nor is it present simultaneously in all parts of the cortex, but sweeps across it from before backward. Thus strychninization of band I may result in suppression of the leg-, arm- and even face-subdivisions, starting in the intermediate precentral cortex, then appearing in the immediate precentral, then in the immediate postcentral and finally in the parietal cortex. The second characteristic of band I is that it is "fired" by strychninization of no part of the sensory cortex except band II. Band I apparently is comparable to that area, lying in front of L. and A. 6 of the macaque's brain, from which eye movements can be elicited and the local strychninization of which gives suppression of the electrical activity within the sensory cortex (15).*

Band II. The primary characteristic of this band is that it is a region, whose strychninization results in the most extensive "firing" obtainable from any region of the sensory cortex. Not only does it "fire" the entire precentral cortex and the entire postcentral sensory cortex, except for band IX, but it also fires band I and fails to respect functional boundaries. For instance: Face II can "fire" even leg X; arm II can "fire" the whole of the arm-subdivision (except IX) and portions of the leg- and face-subdivisions.

It is perhaps an oversimplification to treat band II as a single entity, for in a given hemisphere one can obtain from some portions of band II the "firing" of band X without that of the intermediate regions and by strychninization of another portion of band II "firing" of the intermediate region without "firing" of band X and by strychninization of other portions an admixture of these two results. However, the present evidence does not allow us to make any more definite statements on this score.

Band II is the most anterior portion of the sensory cortex by the criterion used. It is obviously comparable to area 6 of the macaque's sensory cortex, with respect to the distribution of the strychnine spikes, especially the failure to respect functional boundaries.

Band III. This band is a suppressor region, *i.e.*, its strychninization gives a widespread suppression of electrical activity in the sensory cortex and in bands I and XI. The effect on itself is an initial spiking followed by suppression of its electrical activity. The suppression obtainable from this band violates functional boundaries. Its properties and its position immediately behind band II indicate its homology to area 4-s of the macaque's sensory cortex. An apparent difference from area 4-s of the macaque is that,

* In one instance strychninization in band I besides "firing" itself, questionably suppressed itself.

in that animal, we were never able to obtain suppression without "firing" of postcentral areas, whereas in the chimpanzee we have obtained pure suppression in 2 out of 15 cases of suppression from band III. Moreover, the "firing" of some of the regions in the cases of mixed suppression from band III was clearly referable to extension of the strychnine into the adjacent bands.

Bands IV and V. These two bands occupy the cortex between band III and the fissura centralis. In their primary characteristics these bands have in common that their strychninization results in "firing" of other areas, not in suppression. It is, however, necessary to distinguish two bands in this region, band IV and band V, because the strychninization within the frontal portion, band IV, gives a distribution of strychnine spikes different from that following strychninization within the posterior portion, band V, and because the distribution of the strychnine spikes following strychninization of some of the postcentral bands (VIII and IX) is also different in regard to bands IV and V. (See Fig. 4.) The position of bands IV and V is roughly comparable to area 4 of the macaque and a simultaneous local strychninization of the two of them gives results closely comparable to those following local strychninization of the macaque's area 4. Moreover, these bands IV and V are that region of the cortex of the chimpanzee, ordinary faradic stimulation of which elicits prompt, discrete movements, and which cytoarchitectonics pronounces to be the area giganto-pyramidalis. Thus, in the chimpanzee it has been necessary to make, in this region, a distinction which thus far we have not been able to discern in the macaque.

Band VI. This band is a "firing" band. Strychninization within this band besides "firing" itself can "fire" bands III, IV, V, VII, VIII and X. We have never observed any "firing" of bands II or IX following strychninization of VI. The "firing" obtainable from this band is the most extensive of the "firings" obtainable from the postcentral censory cortex.

Band VII. Strychninization of this band results in suppression of electrical activity throughout the entire sensory cortex and even outside—bands I and XI. The electrical activity of band VII itself shows an initial "firing" followed by suppression. In 2 out of 13 cases pure suppression was obtained.

Band VIII. This band is a "firing" band, affecting of the precentral cortex only band V.

Band IX. This again is a "firing" band, which can be differentiated from band VIII in that its strychninization does not "fire" band V, but "fires" band IV. With respect to the postcentral cortex, it should be noted that band IX does not "fire" X, whereas strychninization of band VIII does "fire" X. Moreover, band IX is unique in the postcentral sensory cortex insofar as it is "fired" only by strychninization within it. The question mark re "firing" of this band from band X denotes uncertainty whether the strychnine responsible for this "firing" of the latter band had not transgressed into band IX.

Band X. Again this is a "firing" band, strychninization of which "fires"

only band III of the precentral cortex and, of the postcentral sensory cortex, only itself. This band of the postcentral sensory cortex is unique in that its "firing" does not respect functional boundaries, *i.e.*, does not remain within the subdivision locally strychninized. Strychninization of leg X can "fire" leg X *and* arm X and leg III and arm III. It also "fires" band XI, outside the sensory cortex. We say "outside the sensory cortex" because band X being the most posterior region to "fire" into the sensory cortex, by this criterion, is the most posterior of its constituent bands. With respect to homologizing the postcentral bands with the postcentral areas of the macaque's sensory cortex we wish to take up the discussion of these bands together, since we have not as yet been able to make a comparable differentiation in the macaque. All we can say definitely at present is that in both the the chimpanzee and the macaque there exists a postcentral sensory suppressor band—band VII of Fig. 3 and 4—behind which lies a region which in both animals "fires" into the precentral sensory cortex. In view of the findings in the chimpanzee the functional organization of the sensory cortex of the macaque's brain is under reinvestigation with cytoarchitectonic controls. Not until this work is completed, do we dare to say anything in regard to homologization of the more anterior parts of the postcentral sensory region of the chimpanzee and macaque.

Band XI. This band lies outside the sensory cortex by the criterion that strychninization within it never "fires" any portion of the sensory cortex. Its primary characteristic is that strychninization within it suppresses the entire sensory cortex and even band I in front of it.

For the arm-subdivision we have no evidence that strychninization of band XI besides "firing" itself may also later suppress itself; for the leg-subdivision (chimpanzee 9) the sequence of these two phenomena was observed.

In the re-investigation of the macaque's cortex mentioned above special attention was paid to the question whether in this animal a region outside the sensory cortex, comparable to band XI of the chimpanzee's brain, exists. The investigation has proceeded far enough to show that this is the case and to state that these bands in the two species correspond closely as to position and shape. This statement holds also for the manguebey's brain.

It has been found that the posterior border of the sensory cortex in the chimpanzee and, with it, the location of band XI on this brain in relation to the fissura parieto-occipitalis externa and the end of the first temporal sulcus shows great variability. In the chimpanzee on which the diagram of the sensory cortex in the preliminary note (Fig. 1) was based this cortex extended clear to the parieto-occipital fissure. In all the animals upon which this paper is based it was found that the posterior border of the sensory cortex lay in front of this fissure and even that in some hemispheres band XI—outside the sensory cortex—did not extend as far back as this fissure. The same variation has subsequently been found in the macaque. These findings suggest that band XI and its homologue in the macaque may well be area 19 of Brodmann.

Interesting is the posterior "dud" area bulging into the sensory cortex between the end of the fissure of Sylvius and the first temporal sulcus. The diagrams of Campbell (4) for man and the subhuman apes show a region of essentially similar configuration, belonging, according to Campbell, to the temporal lobe bulging into the parietal cortex, the posterior end of his "auditopsychic" area. We wish to point out that it was not until we were writing this discussion and trying to make the homologizations that we became aware of the remarkable coincidence between this point in our physiological findings and Campbell's histological studies. A similar "dud" area has subsequently been found in the macaque in the vicinity of the end of the fissura Sylvii and anterior to the first temporal sulcus.

In conclusion it should be emphasized that the diagram of the functional organization of the chimpanzee's sensory cortex as given in Figs. 3 and 4 shows the maximum of "firing" and suppression observed, not in one animal nor following one strychninization, but that it gives the synopsis of all data collected.

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UNIT FOR SENSORY RECEPTION IN CORNEA

WITH NOTES ON NERVE IMPULSES FROM SCLERA, IRIS AND LENS

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WITH THE ADVENT of unitary analysis of activity in the nervous system, heralded by Adrian and Bronk's (1928) paper recording the impulses carried by single fibers isolated in peripheral nerves, a method became available whereby the terminal distribution of a single afferent fiber might be disentangled from those of its associates, identified as a unit, and so examined. This terminal, together with its fiber, cell body and central processes, could be considered the sensory equivalent of the neuro-motor unit. Nevertheless the basic problem: what constitutes the functional unit for sensory reception: still remains largely unsolved.

To review the perplexities: When a single nerve fiber terminates in a single encapsulated ending, Pacinian corpuscle, muscle spindle, or other, the nerve tissue within the encapsulation clearly comprises the entire receptive terminal of the neuron. This, the simplest, is also the rarest case, but the innervation of some of the frog's spindles examined by Matthews (1931) probably conformed with this design. When, however, a single fiber innervates two or more such corpuscles or spindles, what is to be considered the unit nerve ending: all the terminal tissue of one nerve fiber or the separately encapsulated portions of terminal tissue? If the multiple end-organs are dissimilar, as may be the case (Hines and Tower, 1928; Woollard, 1936), qualitative as well as quantitative considerations arise. When two or more nerve fibers enter into one encapsulated end-organ, the problem presents three possibilities. The separate fibers may derive from the same fiber farther back. If not, the one may be afferent and the other efferent. If both are afferent, the problem remains theoretically simple if the two neurons remain separate. The end-organ may be then considered compound, and suspect, as in the case of some mammalian spindles, of serving diverse sensory functions. If, on the other hand, the two neurons fuse in their terminations, a condition which has been often suspected but never unequivocally proven, then from a physiological standpoint at least the problem is complicated indeed.

Still more difficult of definition, however, is the organization in unencapsulated sensory innervations. In these, nerve fibers enter into plexuses or ramifications, perhaps with terminal knobs or loops or small skeins, to be distributed over unascertained areas. Such ramifications are the most widespread form of afferent innervation of both skin and viscera, and probably the phylogenetic prototype. Yet unless by the fluke which gives a complete Golgi impregnation of one nerve cell body and its processes standing out in the midst of its less stained neighbors, histological techniques will be severe-

ly taxed to demonstrate the neuron units in such organization if the unit is distributed over more than a few square millimeters. A plexiform arrangement of nerve fibers may be traced over a large area by silver, or better by methylene blue staining, but the individual neurons can scarcely be kept track of. This obscurity of the neuron unit has fostered a tendency on the part of anatomists to consider the so-called free nerve endings in terms of a terminal reticulum or network in which syncytial continuity of individual neurons is at least suspected. Yet such a viewpoint is as unfounded on anatomical fact as the contrary supposition of individual discreteness, and considerably less acceptable *a priori* because of the validity of the neuron doctrine at the outset of the embryological development of this afferent innervation together with the rest of the nervous system.

Since the problem became open to examination by physiological procedure, however, the neuron unit in such a ramification has been delimited in three sites, with no indication in any that the units are other than discrete. Adrian, Cattell and Hoagland (1931) have outlined on the frog's skin areas of terminal distribution of single afferent neurons sensitive to touch which Rubin and Syrocki (1936) later identified with free nerve endings in the epidermis. The areas defined ranged from 4 to 100 sq. mm. but actually, since the demonstration depended on bifurcation of sensory axons close to the dorsal root ganglion, the two branches then diverging into different divisions of the spinal nerve, the terminal field outlined for one branch was presumable only a portion of the fiber's total field. In the frog's viscera the terminal distributions of single afferent fibers have been worked out by myself (Tower, 1933). These were surprisingly large, often covering 2 or 3 sq. cm. and not infrequently twice that area. In contrast, the fields of presumed touch fibers in the cat's tongue examined cursorily by Pfaffmann (1939) were fairly small, ranging around 5 mm. in diameter.

The mammalian cornea exposes for examination an uncomplicated field of the ramifying or plexiform type of innervation. The nerve fibers entering into this innervation, all of which is considered, though without proof, to be afferent, are in large part myelinated, but lose their myelin sheaths as they pass from the periphery toward the center. The fine unmyelinated ramifications of these fibers form a plexus in the connective tissue with terminal twigs or knobs or loops or brushes or fine skeins, and with branches penetrating into the epithelium where they may form a second plexus. Within these plexiform arrangements of fine unmyelinated nerve fibers, which have been described and illustrated by Dogiel (1890), Attias (1912), Boeke (1935) and others, there is no anatomical cue to the neuron units. Except close to the sclero-corneal junction, no encapsulated endings are present. The cornea thus invites the attempt to outline the neuron units in a terminal ramification by physiological procedure, and to attack the problem of the discreteness or confluence of these. To this end arrangements were made to amplify and record action potentials in the long ciliary nerves of cats in conjunction with stimulation of the cornea. Ultimately the investigation was extended to other parts of the eyeball.

PROCEDURE

The cats were decerebrated, one orbit unroofed, the 2nd to 6th cranial nerves cut extracranially and the ciliary ganglion removed. The long ciliary nerves were freed from the surrounding tissue and cut as far centrally as possible, often yielding more than 2 cm. for lead. The eyeball was left in its bed after trimming off the conjunctiva at its reflection from the eyeball. To interfere with circulation as little as possible, both vertebral arteries and the carotid of the side under investigation were occluded usually only during the decerebration. The other carotid was ligated. To fix the eyeball, a fringe of conjunctiva was either sewed to a ring fitting the corneal margin; or a perforated button was inserted behind the cornea through a slit along the sclero-corneal junction, with or without the ring lightly clamped in front. Such a button must be removed at frequent intervals to allow free irrigation of the posterior surface of the cornea. Often no device was used. Throughout the experiment the animal was kept in a warmed and humidified metal cage which served also as electrical shield.

For stimulation the following were employed: a set of von Frey needles ($\frac{1}{8}$ to 10 gm.); a corresponding set of hairs (2 to 20 gm. per sq. mm.); a mechanical stimulator delivering the prick of a cactus spine with variable intensity calibrated in grams and with 3 dimensional spatial control; and blunt glass rods. Pinching and tearing were also resorted to.

The action potentials were led off through silver, silver-chloride, ringer, brush electrodes to a condensor-coupled amplifier and Matthews oscillograph, and photographic records were made.

The long ciliary nerves were used entire to lead from when fine filaments were present or when thick, reduced by about half. In a number of experiments, however, the active fibers of one of these nerves were reduced to two or three, and for this skillful manipulation I am indebted to Dr. D. W. Bronk. These will be referred to as "few fiber preparations." For the gross anatomy of the cat's long ciliary nerves, which is extremely variable, reference may be had to Christensen (1936). According to Windle (1926) they are composed of non-myelinated and small myelinated fibers all under 7μ in diameter. Anticipating the simplest results of the present study: Of the two main divisions of long ciliary nerves the medial supplies the medial and inferior portions of the cornea and the lateral the lateral and superior portions, with overlap of several millimeters at the center and along these territorial boundaries.

OBSERVATIONS

The nerve impulses from receptors in the cornea constituted a graded series from moderately large to quite small. To what extent this apparent gradation was a function of fiber size, to what extent of more or less favorable situation at the lead, it is impossible to say. Of necessity attention focused on the larger members of the series, the smaller being progressively lost track of as they approximated to the instability of the base-line. All the activity which is the material of this report took the form of spikes in the records. By comparison with Zotterman's (1939) records from stimulating the cat's skin, purporting to show activity in unmyelinated fibers, all these spikes presumably represented activity in myelinated nerve fibers.

Leading from fine filaments of long ciliary nerves the responses obtained from the cornea using the different forms of mechanical stimulation were essentially similar: trains of impulses of rapidly diminishing frequency, or occasionally with threshold stimulation a single impulse only. Initial frequency and duration of the discharge were functions, both, of the intensity of the stimulus. Thereafter with continued stimulation the discharge diminished, sometimes to cease entirely in a few seconds, sometimes to establish a level of activity sustained for as long as the stimulation. With all but the lightest stimuli, removing the stimulus commonly caused a second small

outburst. Not infrequently, when the number of fibers responding was small and the individuals identifiable, certain fibers adapted completely while others did not, to the same stimulus. The $\frac{1}{8}$ gm. von Frey needle was only once effective, the $\frac{1}{4}$ rarely, the $\frac{1}{2}$ gm. usually; but threshold might be as high as 1 gm. in a preparation which gave no other sign of deterioration. The hairs yielded effects similar to those obtained with the needles except that threshold was rarely less than 4 gm.

Isolated by attack on the nerve, one nerve fiber of the type yielding fairly large impulses was found to be distributed over roughly a quadrant of the cornea and usually over the adjacent 1 to 3 mm. of sclera. Certain fibers, those with the largest spikes, covered an even larger territory, very nearly one half the cornea and the adjacent sclera back almost to the equator of the eyeball. When a fringe of conjuctiva remained, fibers of corneal distribution were also found distributed there, but the extent of such spread was not worked out. Within this large area of 50 to 200 or more square millimeters were islands not supplied by the fiber in question, but perhaps in a two fiber preparation by the second of the survivors. The lowest threshold and slowest adaptation were usually 2 or 3 mm. inside the sclero-corneal junction in the midst of the fiber's field, and both increased irregularly toward the periphery in all directions. Rapid adaptation even to the limit of a single impulse characterized the periphery more than did high threshold. Considering the large area of distribution of the single fiber and the slight deformation produced by all except the strongest stimuli, only near the periphery would the deforming action overstep the limits of a fiber's field. Therefore the greater central sensitivity must represent either a greater central concentration of nerve-ending tissue, or more strategic situation, or degradation from center to periphery of the excitability of the nerve tissue itself. Fibers carrying the smaller impulses seemed to have more restricted distribution, but their identification as individuals was never so certain as with fibers of larger impulse size.

Threshold for the single fibers covered the same range as threshold for a whole nerve. Frequency, on the other hand, was usually very much less. Yet for the first hundredth second of response to a fairly strong stimulus, frequencies in excess of 500 per sec. are on record for unquestionably single fibers; and to moderately strong stimulation such as the 4 gm. needle, frequencies of 220 per sec. for the first fiftieth second; while the 2 gm. needle commonly evoked 3 impulses in the first fiftieth second. At threshold and up to twice threshold, however, the discharge for the first one-fifth second was fairly constant, and rarely in excess of 40 per sec. In the next two-fifths second it dropped off, either to cease entirely, or to establish a level of continued discharge at 1 to 8 per sec. After the stimulus was removed, a corneal ending which had not previously been spontaneously active showed no tendency to continue discharging.

Rate of adaptation was a function both of the site and of the intensity of stimulation. Adaptation might be complete after the discharge of one im-

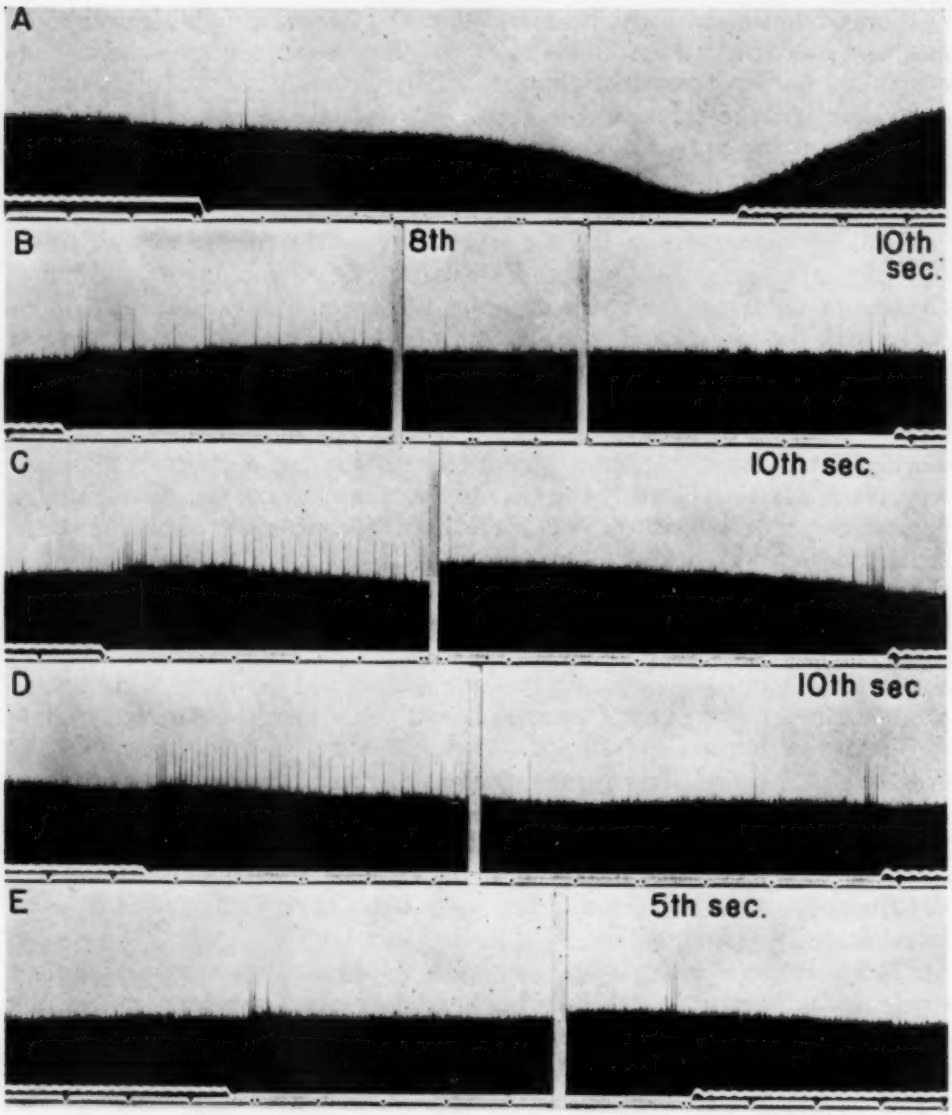

FIG. 1. Response, adaptation and fatigue to a series of stimulations of increasing strength applied by the mechanical stimulator to the most sensitive spot in the corneal field of a fairly large fiber. "Few fiber preparation" of a lateral long ciliary nerve. Duration of stimulation shown by upper signal; time in 0.2 sec. by lower.

a, contact: b, 1 gm. for 10 sec. last response in the 8th sec.; c, 4 gm. for 10 sec. last response in the 9th sec.; d, 8 gm. for 10 sec. adaptation still incomplete; e, 1 gm. for 5 sec. adaptation almost at once.

pulse only with any effective stimulation on the periphery of a fiber's field, or with contact in the most sensitive central area (Fig. 1A), whereas with stronger stimulation in this area it might require ten seconds or longer

(Fig. 1B–D). In the central area of a fiber's field, beginning at threshold and increasing the intensity of stimulation increased the duration of discharge more conspicuously than the initial frequency (Fig. 1A–D); that is, it slowed adaptation. Both deterioration and fatigue operated faster and more effectively to accelerate adaptation than to reduce the initial response. Though clearly illustrated in Fig. 1 by comparison of B with E, this effect of fatigue was even more striking in a longer series of 100 stimulations at 1 gm., 1 sec. on and 2 sec. off. Throughout such a series the initial burst retained very nearly its original proportions, but adaptation speeded up until it followed immediately on the initial burst. Series timed with the periods of rest and of stimulation approximately equal exhausted the initial response as well as the continued. For the central regions of active fibers and for equivalent stimulation, adaptation was always slower at the start of an experiment than toward the end. These observations create the impression that the normal corneal sensory mechanism is characterized by slow or incomplete adaptation in the central most sensitive portions of the terminal distribution of individual nerve fibers, in contrast with exceedingly rapid adaptation on the periphery and in the most superficial ramifications.

Within the terminal ramification of one nerve fiber local conditions influenced both the initial frequency and the duration of discharge evoked by a given stimulation. Denial of access of aqueous humor to one part and not to another raised threshold and speeded adaptation locally. This was brought out by the use of buttons with various sized perforations to back the cornea, for the cornea over the solid parts rapidly became unresponsive while that over the holes remained active. The gradual deterioration wits time also attacked the ending irregularly, though with a usual progressioe from the center of the cornea toward the sclera. At best, however, adjacent parts of a fiber's field were rarely equally responsive. From point to point the discharge varied, though always with a general gradient of decreasing activity from a central most sensitive region toward the periphery in all directions.

Adaptation and fatigue were also spatially restricted processes in healthy preparations. Thus a series of stimuli which rapidly produced fatigue or cumulative adaptation if directed to one point, failed to do so if spaced a millimeter apart. With continued moderately strong stimulation to which adaptation was complete the adaptation affected such a limited area that a second stimulus as close as possible, perhaps a millimeter, from the site of the first, provoked a fresh vigorous discharge over the same nerve fiber. The mechanical stimulator was used for the continued stimulation; a von Frey needle for the intercurrent.

The separate regions of one nerve terminal were nevertheless not completely independent; on the contrary the whole terminal appeared to be conditioned by each of its parts. From time to time preparations were obtained in which a nerve fiber with corneal distribution was spontaneously and rhythmically active 1 to 8 times per sec. sometimes for hours. Such

"tickers" were readily identifiable as individuals when the nerves were cut down, although leading from a whole nerve, their individuality tended to be submerged. One three-fiber preparation had two such "tickers," one ephemeral, the other performing for 8 hours at a rate falling from 5 to 7 per sec. at the start to 1 to 4 per sec. at the end. This latter is the fiber active in Fig. 2 Such spontaneous discharge was never absolutely regular even over very brief periods of time, and was subject to the same conditions as deliberately excited action, slowing and ceasing when the circulation of blood or aqueous humor was interfered with, or examination too long continued, and being restored by rest and care. Although this indicates a corneal origin for the spontaneity, which was verified in two instances by excising the cornea, whereupon it ceased, deliberate attempts to provoke spontaneity by damaging the cornea were not successful.

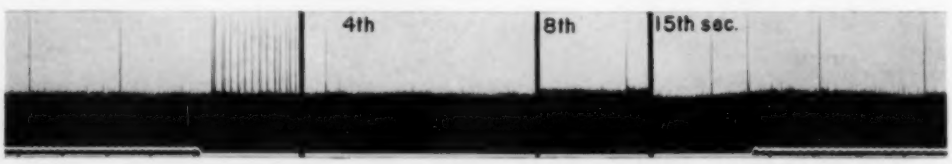

FIG. 2. Spontaneous activity in a fiber with corneal distribution, and inhibition of this by 4 gm. stimulation applied with the mechanical stimulator to the central region of the fiber's terminal. Inhibition was complete from the end of the 3rd to the middle of the 8th sec., and the control rate of spontaneous discharge was reestablished only in the 12th sec. Few fiber preparation of a lateral long ciliary nerve. Duration of stimulation shown by upper signal; time in 0.2 sec. by lower.

Stimulation of the corneal terminals of such a "ticker" elicited the usual outburst of impulses, but following this, either after the stimulus was removed or after adaptation to continued stimulation, the spontaneous firing temporarily slowed or ceased. With strong stimulation which was not adapted to, the depression of spontaneity became evident only after the stimulus was removed. In one record the spontaneous firing regained the control value only 25 sec. after the "off," while suppression for 5 to 10 sec. was frequent. Figure 2 summarizes such inhibition of 4.5 sec. duration resulting from moderately strong stimulation; while a more concise record of a briefer instance has already been published (Tower, 1935) in a preliminary report. Stimulation anywhere within the extensive terminal field of the spontaneously active fiber produced the depression and in proportion only to the volume of the discharge called forth, while excitation of other fibers within the area had no such effect. The inhibition was most active with the preparation in best condition, being then recorded from as little as two stimulated impulses. It was certainly effective, that is as outright inhibition, only against the presumably minimal excitation which fired spontaneously and not against a stimulus such as the 1 gm. needle applied in the inhibitory period, though a small reduction of response to such a stimulus would scarcely have been appreciated. In the opposite direction, on rare occasions toward the end

of an experiment when a "ticker" was firing feebly and irregularly, weak stimulation in the fiber's field appeared to increase and to steady the spontaneity, and sometimes even to reinstate it after it had lapsed.

The inner surface of the cornea, exposed by a cut along the sclero-corneal margin in its upper half, responded on stimulation applied as to the outer surface with a discharge of similar characteristics, but of lesser volume.

Discussion

By isolation of nerve fibers in the nerve trunks the terminal ramification of the single sensory fiber to the cornea stands out as a unit distributed over 50 to 200 or more square millimeters of cornea and adjacent sclera and conjunctiva. The sharpness of outline of the single fiber's field, the occurrence of islands with other innervation within that field, and the different patterns of terminal distribution of individual nerve fibers all testify to the composition of the total terminal plexus as an aggregate of units and against the existence of a syncytial terminal nerve net entered into by numbers of fibers. Meshwork of the order of magnitude figured by Boeke (1935) for example, 100μ more or less in diameter, must therefore represent structure within the total ramification of the unit neuron.

If the terminal units thus outlined on the cornea and sclera include all the terminal tissue of one nerve fiber, then they constitute together with their cells and fibers, neuro-sensory units on a par with the neuro-motor units. But only by leading off immediately adjacent to the root ganglion cell and exploring the entire field of distribution of the Vth nerve could the possibility of axon bifurcation be excluded, and not in a lead from the long ciliary nerves. Such axon bifurcation, besides providing the basis for Adrian, Cattell and Hoagland's (1931) experiment outlining the fields of touch fibers in the frog's skin, almost certainly underlay Wernöe's viscero-cutaneous reflex in the fish (1925), and naso-ocular vasodilator reflex in man (1922), while Lewis (1936) has presented evidence which can be interpreted only on the basis of similar bifurcation of axons in his nocifensor system in man. Within the maxillary division of the Vth nerve, for example, a single afferent neuron thus appears to have terminal ramifications both in the mucous membrane of the antrum and in the skin of the face. With this reservation in mind, however, and with the further reservation that the known spread of some fibers onto the conjunctiva was not fully explored, the terminal units outlined for the cornea represent neuron units of afferent innervation.

The question still remains, however, what constitutes the functional unit for sensory reception,—each of the numerous small terminals described by the anatomist on one nerve fiber, or the neuron unit of terminal ramification? The evidence presented shows that adaptation is quite localized within the terminal ramification, together with fatigue and other conditions influencing general responsiveness. Yet some aspect of the receptive activity, presumably the propagated impulse, seems to spread throughout the terminal ramification to alter excitability elsewhere than at the site of original

stimulation. With point stimulation, although the mechanical deformation can scarcely act on more than a small fraction of any neuron unit terminal as determined by the site and strength of the stimulus, still when mechanical stability was achieved the train of impulses was quite regular in the individual fiber with all strengths of stimulation, making it unlikely that parts of the unit were firing off independently.

Regulation whereby haphazard firing may be prevented, and the train of impulses evenly spaced with a frequency conditioned both by site and by intensity of stimulation can be conceived in terms of structure. Adrian (1932, p. 29) made the suggestion that rapid and slow discharges may not arise from the same point; that there may be a gradual transition from nerve fiber to nerve ending with a gradual slowing of time relations, and that an intense stimulus may take effect at a point where recovery is rapid. Translating this into morphological concept: If the unit terminal is an arborization wherein a stem fiber, which may or may not be myelinated, divides into branches successively finer out to the ultimate free end or closed mesh, with or without mesh connections in the previous orders of branching, then a strong stimulus near the point of entrance of the nerve fiber into its terminal ramification might be expected to push frequency to the limit permitted by the absolute refractory period of the fiber itself, and even to infringe on the relative refractory period. The maximum frequency of 500 per sec. in the response from the cornea suggests such limitation. In support of this view highest frequency, lowest threshold and slowest adaptation were usually found in individual fiber terminals, not at the center of the cornea, but a few millimeters inside the sclero-corneal junction where anatomical studies have described the myelinated nerve fibers as loosing their myelin sheaths and commencing to ramify. Since the nerve fiber always begins to arborize fairly deeply, the deformation of a feeble stimulus at that site could not be expected to reach the trunk fiber, but only the more strategically situated and finer superficial ramifications. If fineness imposes slowness, the slow train in response to weak stimuli may be thus determined. On the periphery of a large field, many millimeters from the point of entrance of the nerve fiber, intense stimulation could be expected to affect only the outlying parts of the arborization, again presumably finer and of slower properties. And correspondingly, on such a periphery in the cornea, stimulation, no matter how strong, provoked a brief, widely spaced train of impulses or one impulse only, like threshold or contact stimulation in the center of the field. If the individual arborization becomes intra-epithelial both superficially and on its periphery, a point on which there is as yet no anatomical evidence for the cornea but extremely suggestive evidence for the skin (Woollard, Weddell and Harpman, 1940), this might explain the similar rapid adaptation in the two sites, in contrast with the slow or incomplete adaptation to strong stimulation in the central area. For Hoagland (1936) has related the rapid adaptation of the frog's touch fibers, by comparison with the slow adaptation of deeper lying fibers which presumably serve pain, to the rapid liberation of

large amounts of potassium by deformed epithelial cells and not by the deeper tissues when similarly stimulated. In conformity with this view is the recent agreement of Waterston (1933) and Woollard (1936; see also, Woollard, Weddell and Harpman, 1940) for the human being, that touch is the dominant sensation obtained from the epidermis whereas pain is lodged mainly in the subepidermal levels.

Putting the facts together, the sensory receptor in the cornea emerges as all the terminal tissue of one nerve fiber. This is a unit, activity in any part of which affects the whole. Moreover there is no evidence that activity in this unit influences in any way the activity of spatially coextensive units. Functionally, the corneal sensory mechanism appears as an aggregate of units and not as a continuum. Nevertheless within the unit there are possibilities of correlated structural and functional differentiation such that the frequency and duration of the train of impulses conducted to the central nervous system may be determined not alone by the intensity of stimulation but also by the site. This introduces a new condition into the central evaluation of peripheral stimulation which may permit of central analysis of peripheral locus on other than a one site: one fiber relationship. By central analysis of a pattern of excitation wherein fibers excited minimally encircle fibers more strongly excited, a crude localization may well be achieved, yet the volume of the response from the encircled fibers, or better, the frequency of the discharge in the individual fibers most strongly excited, still serve to signify the intensity of the stimulation as has previously been assumed.

The central portion of the human cornea yields to any form of stimulation, only one sensation. With more than threshold stimulation this is unquestionably painful. Contrary to von Frey's (1894) contention that the sensation is wholly painful, Goldscheider and Brückner (1919) have presented convincing evidence that beneath the pain there is also a feeling of touch or pressure, not as a separate modality but as a second aspect of one sensory experience. The reality of this touch has been clearly exposed recently by the employment of Sjöqvist's operation of tractotomy (cutting the descending root of the Vth nerve in the medulla) for relief of trigeminal neuralgia. Rowbotham (1939) examined two such cases and established that, although the cornea was insensitive to pain, the contact of a wisp of cotton or of a camel hair brush was appreciated as touch. This has been confirmed by Grant, Groff and Lewy (1940). The bifurcating fibers of the Vth nerve become intelligible in this relationship, with their branches terminating respectively in the main sensory (touch) and descending (pain) nuclei of the Vth cranial nerve. The cornea is not, however, peculiar in this conjunction of a touch quality and pain. Heinbecker, Bishop and O'Leary's (1934) study of cutaneous sensibility described prick pain as the affective quality resulting from more than threshold stimulation of a pricking-touch sense. This threshold pricking-touch and its more than threshold pain they distinguished both from familiar modality of touch and from the pain of hot and burning. Correspondingly, Nafe and Wagoner (1937) showed that the central portion

of the cornea which is insensitive to warmth and cold, is also insensitive to the pain of excessive temperature stimulation. Thus sensation from the human cornea seems to be unified in a touch-pain continuum.

The reactions of laboratory mammals to stimulation of the cornea recapitulate those of man. Therefore it may be inferred that the sensation evoked is likewise dominated by pain. The wide extent of the single ending, covering a square centimeter or more, reflects one subjective characteristic of pain sense wherever this is found devoid of specialized touch as in the cornea, glans penis or viscera,—its lack of any but the most general localization. Likewise the initially rapid but then often incomplete adaptation repeats another aspect of the same subjective experience. Bearing in mind Heinbecker, Bishop and O'Leary's (1933) experience with electrical stimulation of human peripheral nerves, that a stimulus of strength more than adequate to call forth pain on repetition, applied as a single shock registers, not as pain, but as prick: the single impulse or very brief train which results from minimal or peripheral stimulation of the cornea, arising perhaps in terminal tissue strategically located in the epithelium, may be suspected of registering as the threshold or background touch, whereas the higher frequency discharges from deeper reaching deformation may certainly be construed as pain.

Conscious painful experience, however, presents two aspects, stimulus pain as from a prick, and the persistent dull ache or pain of injured tissue. Previous attempts to account for the latter phenomenon (Adrian, 1932; Zotterman, 1939) have invoked the unmyelinated pain conducting C fibers. Yet the records from stimulating the cat's cornea are lacking in evidence of very slow impulses and waves such as Zotterman clearly obtained from the cat's skin and ascribed to activity in C fibers,—synchronized in the waves If this may be taken as evidence that non-myelinated fibers have small share in the innervation of the cornea, and the anatomical descriptions of that innervation certainly dwell largely on myelinated nerve fibers as the source, then injury pain must derive from properties of pain endings in general and not from peculiarities of the C fibers alone. In the "tickers," fibers of demonstrated corneal distribution, the steady discharge of 2 to 8 impulses per sec. over a period of hours, a discharge, moreover, which does not prevent response to interpolated stimulation, is just such an activity as might be expected to underlie a continuous dull ache or pain. Thus the properties of the sensory mechanism studied in the cornea, seem to offer peripheral determinants of the central processes resulting in the sensation of pain.

Notes on nerve impulses from receptors in other parts of the eyeball

Sclera. By comparison with the cornea, the sclera posterior to the reflection of the conjunctiva was poorly supplied with nerve fibers gauged by the volume of response to equivalent stimulation, but the form of response to pressure, prick, pinching and pulling was similar everywhere over both cornea and sclera. Over the anterior part of the sclera, the fibers were in

large part those distributed also over the cornea, but each site possessed fibers not distributed to the other. Figure 3a shows a stimulation of the sclera in the region of the equator in which the dominant fiber responding was not known to have other than scleral distribution. The sensibility of the sclera was not appreciably altered by cutting off the cornea and evacuating the entire contents of the eyeball: vitreous, lens, iris, ciliary body and retina; but the more violent of the stimulating procedures applied to the sclera, and perhaps all of them, may very well have involved the chorioid also. Agababow (1904) may be consulted for the morphology of the afferent innervations of sclera and chorioid in which the freely ramifying fiber again predominates.

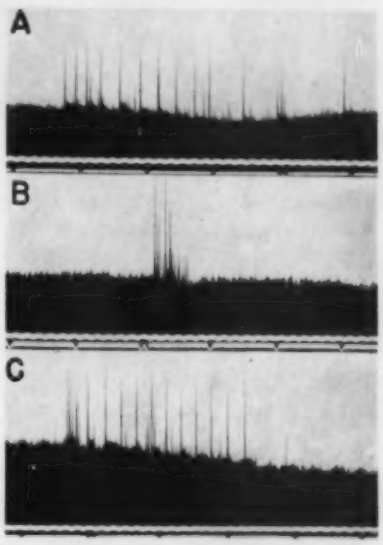

FIG. 3. a, Response to stroking the sclera at the equator of the eyeball with a blunt glass rod. "Few fiber preparation" of a lateral long ciliary nerve. Time 0.2 sec. b, Response to a feeble tug on a thread passed through the medial edge of the iris. Lead from a fine filament of the medial long ciliary nerve. Time, 0.2 sec. c, Same preparation and lead. Response to pressing on the anterior surface of the lens with a blunt glass rod.

Iris. In contrast with the sclera, the iris, exposed by excising either the upper half, or the entire cornea, proved to be exceedingly sensitive. Leading from a fine nerve, the slightest push on the iris with a light von Frey hair, or pull by means of a thread passed through its margin provoked a furious outburst of spikes in which the characteristics of the constituent impulses were obscured. With the lead cut down so that the discharge from the iris was sufficiently scanty to permit examination, the range of impulse size proved to be similar for iris and cornea, but with a predominance of medium to small spikes. Figure 3b illustrates such a discharge.

Lens. By carefully trimming out the iris with a fine scissors, the lens was exposed in situ. While not demonstrably sensitive to prick or to touch with the von Frey needles or hairs, pushing on its anterior surface by means of a blunt glass rod provoked a small outburst of good sized impulses interspersed with a few smaller impulses, the total representing activity in less than half a dozen fibers. In this small discharge, which is illustrated in Fig. 3c, repetitive action of individual fibers was easily recognized. Traction on the lens by means of a thread passed behind it produced a more confused series of medium and small impulses, again of brief duration. Altogether, the lens appeared to be without surface sensibility, but to possess what might be characterized as proprioceptive sensibility in modest proportions. However, since no nerve fibers reach the lens so far as is known anatomically, the receptors in question probably were located in the ciliary body at the attachment of the subtentacular ligament.

Spontaneous discharge and increased intraocular pressure. Spontaneous activity in the long ciliary nerves was a usual feature of the preparations, expecially when fresh and with the circulation in good condition. That the spontaneity originated in the eyeball and not in the nerve trunks, was established by severing the nerves at their emergence from the eyeball. Examined in identifiable fibers, the most conspicuous spontaneous discharge was that already described as the "ticker." A second pattern is illustrated in Fig. 4; repetitive discharge within a period of about one second, of 18 to 24 large impulses, followed by a quiet interval of about 2 sec. The spikes in these discharges exceeded in size any obtained from the cornea, and the discharge persisted after the cornea was removed, and the iris, ciliary body, and lens were shelled out, with timing still as at the outset 3 hours before. However, the greater part of the spontaneous activity, especially that of small impulses, eluded analysis for pattern if indeed pattern existed. Examples of such activity may be seen in all the records.

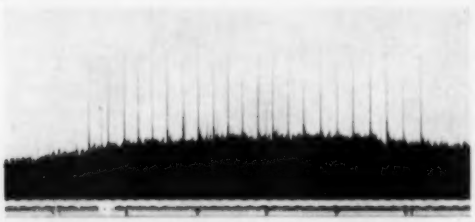

FIG. 4. Spontaneous discharge of large spikes in bursts, and of medium and small spikes irregularly. The contents of the eyeball were evacuated and the cornea excised. Lead from a fine filament of the medial long ciliary nerve. Time, 0.2 sec.

Early in the course of this study it was discovered that when spontaneous activity reached confusing proportions, aspiration of fluid from the anterior chamber of the eye, or relieving the pressure by a small slit behind the sclerocorneal junction, materially reduced the activity, while injecting Ringers fluid or air into either anterior or posterior chamber intensified it or provoked it in quiet preparations. Figure 5 illustrates the sequence of raising and lowering intraocular pressure in an initially fairly quiet preparation. Although this observation has been most striking with the unresolvable spon-

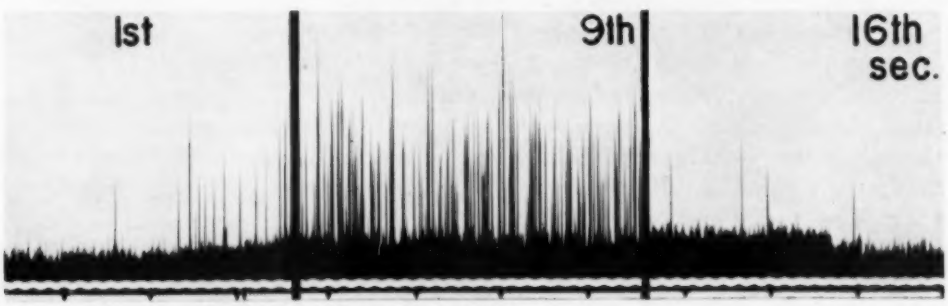

FIG. 5. Response to raising and lowering the intraocular pressure by injecting Ringer's fluid into the anterior chamber of the eye. Total duration of raised pressure, 15 sec. The hypodermic needle was inserted through the medial part of the cornea. Lead from the lateral long ciliary nerve. Time, 0.2 sec.

taneous activity of whole nerve leads, both the grouped discharges of very large impulses which were definitely not corneal in origin, and the evenly spaced ticker discharges of fibers of known corneal distribution shared in the effect. In the former, the number and frequency of impulses in a burst increased and the interval between bursts decreased as pressure mounted. The less conspicuous activity of the tickers was quickly submerged in the massive discharge excited as the pressure mounted, but if the pressure were then abruptly dropped so that that discharge rapidly subsided, the spontaneous activity of the ticker then required some seconds to reappear, a result which had otherwise been obtained only by strong stimulation in the fiber's corneal field. This inhibitory effect was most striking in one of the few fiber preparations, but the very fewness of the fibers remaining to innervate the cornea in this case, and the massiveness of the discharge during the period of raised pressure emphasized that increased intraocular pressure must excite afferent innervation which is largely located elsewhere in the eyeball than in the cornea.

Summary

Arrangements were made for oscillographic recording of action potentials in the long ciliary nerves of cats in response to mechanical stimulation of the cornea. For lead, both whole nerves and nerves cut down until only a few fibers registered were used.

The neuron unit of afferent innervation thus isolated is a terminal ramification extending over a quadrant or more of the cornea and spreading onto the adjacent sclera and conjunctiva. This large terminal is spatially differentiated such that the lowest threshold and highest frequency of response are obtained in the central area, the one increasing and the other diminishing toward the periphery in all directions, while adaptation is most rapid both on the periphery and superficially. Within this large terminal adaptation and fatigue are both localized at the site of point stimulation, but some aspect of the activity, presumably the propagated impulse, spreads throughout to condition activity elsewhere. The total corneal sensory mechanism is an aggregate of such neuron units and not a continuum. Viewing the nerve-ending as all the terminal tissue of one nerve fiber, the properties of this receptor then appear as peripheral determinants of many of the qualities of the sensory experience derived from the cornea.

Some notes are included on afferent impulses excited by stimulating the sclera, iris and lens, and in response to increased intraocular pressure.

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LEARNING AND OTHER FUNCTIONS OF THE HIGHER NERVOUS CENTRES OF *SEPIA*[1]

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INTRODUCTION

SURPRISINGLY little is known about the function of the higher nervous centres of invertebrates. Although much has been discovered about the capacity for learning and other more complex modes of behaviour especially among insects, yet there has been little attempt to reveal the activities within the central nervous system by which such reactions are mediated. This is especially regrettable because of the possibility offered by these centres of discovering something of the changes which occur during the process of learning, which in spite of so much study in vertebrates still remains almost wholly obscure (see Lashley, 1937). Yet in this subject, where great difficulties arise from the special and complex arrangements of the vertebrate nervous system, there is some expectation that comparative studies will yield fruitful results.

The central nervous system of the Cephalopods is especially well suited for such work. The supra-oesophageal centres are large, and there is reason to believe that the behaviour is complex and likely to include interesting types of learning. Moreover the animals lend themselves well to experiment, and the parts of the central nervous system are easily accessible for the purpose of operation.

Divisions of central nervous system

The main divisions of the central nervous system of the Dibranchiate Cephalopods are the paired optic lobes, and the supra- and sub-oesophageal ganglia (Fig. 1). However, each of these major regions is subdivided internally into lobes, which are the true structural and functional units. Some, though not all, of these lobes have been previously described and named (see especially Dietl, 1878: Thore, 1939); but details of their internal structure and fibre connections remain obscure, as does the part which each plays in the behaviour of the animal. For present purposes we may recognize centres of four types, as follows.

Lower motor lobes. The sub-oesophageal ganglia consist mainly of large neurons whose axons run, either directly, or after one further synapse, to

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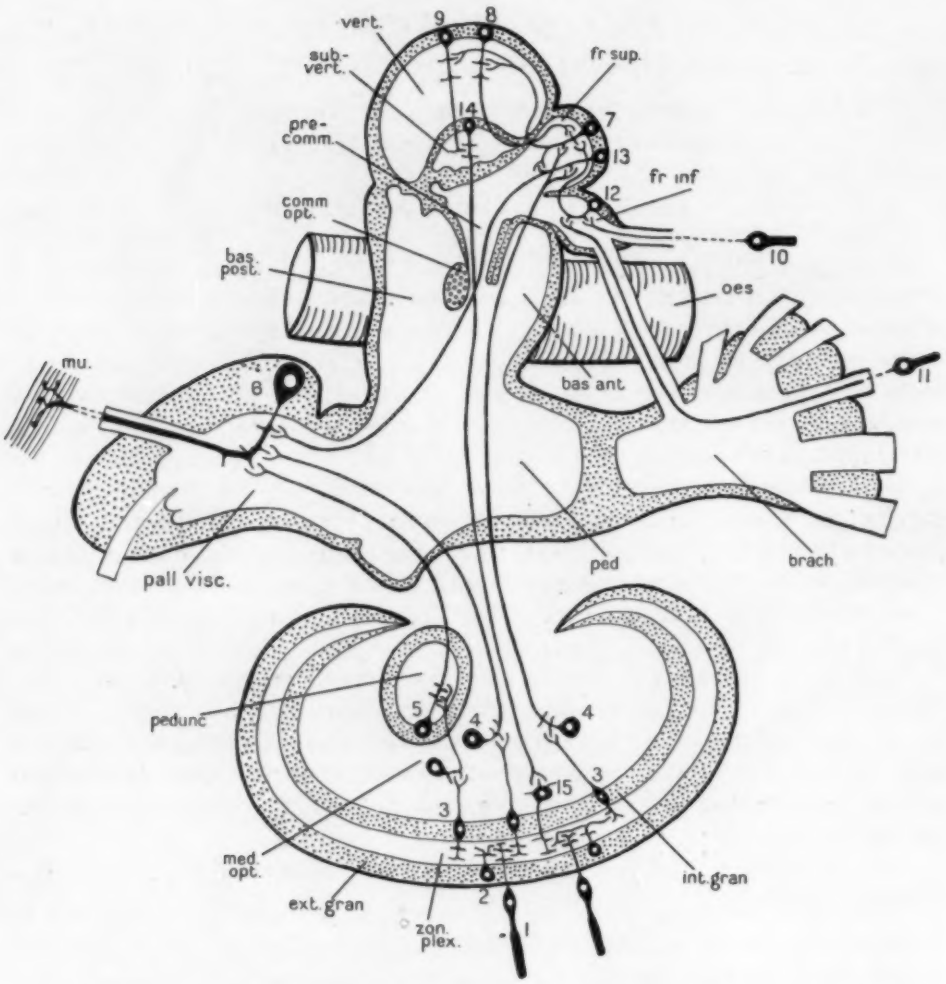

FIG. 1. Diagram to show some of the connections of the verticalis complex of *Sepia*, and its reciprocal relations with the optic lobes. The main outlines drawn from a single sagittal section, but the optic lobes much schematised.*

1, retinal cells; 2, external amacrines; 3, bipolar cells; 4, efferent cells of optic lobe; 5, cell of l. pedunculi; 6, final motoneuron; 7, cell of tractus frontalis superior-verticalis; 8, cell of tractus verticalis-frontalis superior; 9, cell of tractus verticalis-subverticalis; 10, visceral afferent; 11, tactile or chemoreceptory cell of arm; 12, cell of l. frontalis inferior; 13, cell of tractus frontalis superior-precommissuralis; 14, cell of tractus subverticalis-opticus; 15, centrifugal giant cell of internal granular layer.

(*Legend continued on next page*)

* The diagram is based mainly on the work of Cajal (1917) for the optic lobe and original data for the rest. The arrangement is certainly close to that shown but there is still some uncertainty about the following points: a) the exact form of the bipolar neurons 3; b) the connections of the efferent tracts of the lobus pedunculi 5; c) the relations of the sensory tracts 10 and 11 with the neurons 12, and of 7 with 13; d) the connections of the efferent tracts of the lobus frontalis superior 13.

muscles or other effectors (Fig. 1). Thus the arms and tentacles are controlled from the brachial and pedal ganglia, the funnel and eye-muscles from the pedal ganglia, and the mantle, fins and some of the viscera from the palliovisceral ganglion. Electrical stimulation of these centres produces movements of the part innervated, and the movements are local, not synergic. In addition to the large motor neurons, these regions also contain smaller ones whose processes do not extend beyond the lobe itself. Sensory fibres from the skin also end at this level, and the centres are certainly able to act reflexly. After removal of one of these lower motor centres the part innervated is completely and permanently deprived of motor innervation.

The motor neurons of such regions may thus be considered comparable to the ventral horn and other parts of the somatic motor column of a vertebrate, and the lower motor centre as a whole, receiving afferent fibres and containing 'association' and motor neurons, is functionally not unlike the spinal cord.

Higher motor lobes. The more ventral part of the supra-oesophageal ganglia consists of lobes containing neurons of intermediate size, whose axons run to the lower motor centres. In this category are the lobus basalis anterior and posterior (Fig. 1 and 2), a hitherto unrecognised lobe the basalis lateralis, and the lobus pedunculi (="ganglio del pedúnculo óptico" of Cajal, 1917), situated on the optic tract. All of these regions receive many fibres from the optic lobes and they may be considered as higher motor centres. Electrical stimulation of any of them causes movements of large groups of muscles, and after their unilateral removal circling and other forced movements of the animal take place, often in the form of continuous activity, as if their absence had freed the lower centres from an inhibition (Young, unpublished).

The influence of these lobes may therefore be compared in a general way with that of the regions of the mammalian brain which affect the 'tone' of

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(*Continued from preceding page*)

bas. ant.; lobus basalis anterior.
bas. post.; lobus basalis posterior.
brach.; ganglion brachiale.
comm. opt.; optic commissure.
ext. gran.; external granular layer of retina profunda.
fr. inf.; lobus frontalis inferior.
fr. sup.; lobus frontalis superior.
int. gran.; internal granular layer of retina profunda.
med. opt.; medulla of optic lobe.
mu.; muscle.
oes.; oesophagus.
pall.-visc.; palliovisceral ganglion.
ped.; pedal ganglion.
pedunc.; lobus pedunculi.
precomm.; lobus precommissuralis.
subvert.; lobus subverticalis.
vert.; lobus verticalis.
zon. plex.; zona plexiformis of retina profunda.

lower centres, for instance the red nucleus and other parts of the extrapyramidal motor system.

Primary sensory centres. These include the regions directly connected with the main afferent systems, and serving to elaborate the patterns of impulses sent from the periphery. The optic lobes, and especially their outer portions, the 'deep retina' (Fig. 1), are the most conspicuous formations to be placed in this section, but there are also olfactory lobes on the optic stalk (Young unpublished), and perhaps other regions which could be considered of the same nature. This type of centre is not always clearly marked off from

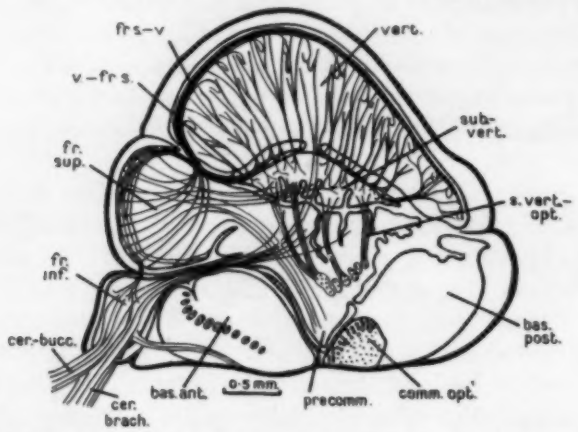


FIG. 2. Semi-diagrammatic view of median sagittal section of supra-oesophageal ganglia of *Sepia*. Outlines drawn from a single section, details schematic.
cer-brach.; cerebro-brachial connective.
cer-bucc.; cerebro-buccal connective.
fr. s.-v.; tractus frontalis superior-verticalis.
s. vert.-opt.; tractus subverticalis-opticus.
v.-fr. s.; tractus verticalis-frontalis superior.
Other lettering as in Fig. 1.

the previous one. The function of such a centre is to allow interaction between the impulses coming from the various parts of the receptor with which it is connected, so that reaction to shape or other qualities of stimulation may take place (see Young, 1938). Faradic stimulation of the centre of the optic lobe of *Sepia*, from which the processes of large cells pass to both supra- and sub-oesophageal regions (Fig. 1), produces definite movements, such as a general darkening or movements of the mantle or fins. But faradisation of the outer portion of the lobe usually produces no movements, presumably because so crude an agent as this stimulation is unable to simulate that patterned mode of activity by which this region normally controls the lower neurons.

Correlation centres. The highest centres, occupying the top of the supra-oesophageal ganglia, consist of very small cells, and are not directly connected with any single receptor or with the lower motor centres. These are the lobes with which the present work is mainly concerned, namely those

called by Dietl (1878) lobus frontalis superior and lobus verticalis, and the region below the latter which will here be called lobus subverticalis (see Fig. 2). These three are intimately connected, and may be collectively called the *verticalis complex*.

It was shown by Bert (1867) and von Uexkull (1895) that these regions are 'silent' areas, whose electrical stimulation produces no motor response. This has been confirmed in *Sepia* during the present work. Faradic stimulation of the lobus verticalis or frontalis superior with a monopolar electrode and a strength of shock considerably greater than that which produces responses from the lower centres produces no visible movements or changes of colour. The results of such experiments must however be accepted with some reserve, since it is possible that the brief shocks produced by an inductorium are unsuitable for stimulating such small fibres.

Study of the connections of the verticalis complex of ganglia throws further light on their function as 'higher centres' since it shows:—(i) that they provide opportunity for the interaction of impulses from various receptor fields; (ii) that they have no direct connections with lower motor centres; (iii) that there are elaborate reciprocal connections between and within the lobes such as would allow of the presence of self-re-exciting chains of activity (see Young, 1938).

Connections of lobus frontalis superior. The mechansim for the interaction of sensory impulses of various types is well seen in lobus frontalis superior (Fig. 1 and 2). This is approximately of kidney shape, as seen in sagittal section, having a thick layer of cells over its anterior surface. The axons of these cells run across the neuropil which occupies the centre of the lobe, and here they are crossed by layers of fibres from sensory sources, producing a characteristic criss-cross appearance. The tracts entering the lobe come from at least four sources, namely:—(i) optic lobes; (ii) skin of arms and tentacles; (iii) receptors around the mouth and perhaps from the gut, by way of buccal ganglia; (iv) lobus verticalis (see below). The discharge of the fibres issuing from lobus frontalis superior is presumably controlled by the combined action of these various sets of fibres, though the exact manner of the interaction, and the significance of the positions of the various layers, remain very interesting subjects for future investigation.

The fibres emerging from the 'hilus' at the hind end of lobus frontalis superior divide into three bundles passing to (i) lobus verticalis; (ii) lobus subverticalis; (iii) higher motor centres at the base of the supra-oesophageal ganglia by way of an undescribed region to be called lobus precommisuralis (Fig. 2).

Connections of lobus verticalis. The opportunities for the formation of self-re-exciting chains of activity are well illustrated by the connections of lobus verticalis (Fig. 1 and 2). This has a thin outer layer and a very large central mass of neuropil. The axons of the cells of the outer layer run downwards across the neuropil, giving off numerous axonic collaterals, and then collect into bundles which pass through into lobus subverticalis and either

end there or turn forwards to form the tract running to lobus frontalis superior which has already been mentioned. The main bundle of fibres entering lobus verticalis is that which arises in lobus frontalis superior. The two lobes can thus certainly influence one another reciprocally, and it is not unlikely that they can do so continuously, setting up a self-re-exciting system. The exact courses of tractus frontalis superior-verticalis and tractus verticalis-frontalis superior which complete the chains are shown in Fig. 3.

The existence of this type of circular connection was the starting point of the experiments to be described below, since it was suggested (Young, 1938) that possibly the cycle of activity is set up when impulses from various afferent sources interact, and that the maintenance of such cycles constitutes the

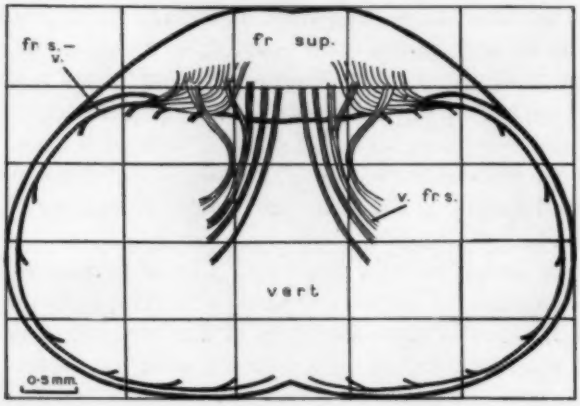


FIG. 3. Horizontal view of l. frontalis superior and l. verticalis of *Sepia*, showing the tracts connecting them with each other. For explanation of the co-ordinates see p. 503. Lettering as in Fig. 1 and 2.

basis of learning. It is not necessary here to recapitulate the details of the scheme originally proposed, but it may be noted that in addition to the cycle between lobus frontalis superior and lobus verticalis, the anatomical arrangements allow for a second and larger one, enclosing the first. For fibres from the lobus subverticalis run to the optic lobes, from which, as already explained, a large bundle passes to lobus frontalis superior. The activities of the verticalis complex can thus influence the discharges of those neurons of the optic lobes which run to the suboesophageal centres either direct or via lobus pedunculi.

The existence of these reciprocal connections must be of fundamental importance in the working of the centres, but it must not be forgotten that in the masses of neuropil lie many cells whose axons do not extend beyond the limits of the lobe in which they arise. The activities of such complex centres can hardly be wholly described in such simple terms as those employed above, which interpret all nervous function in terms of propagated nerve impulses. Yet perhaps no fundamental modification of the scheme pro-

posed would be necessary should we come to understand that masses of nervous tissue such as the neuropil of these lobes function by giving local rather than propagated responses when impulses are fired into them, such local responses serving to change the thresholds of the efferent fibres which issue from the mass.

Our purpose in the present work has been to make a first exploration of the functioning of these regions by the crude methods of stimulation and extirpation. In particular we have attempted to discover what effect on the behaviour, and especially on the powers of learning, is produced by the removal of lobus verticalis, or such part of it as would prevent its reciprocal excitation with lobus frontalis superior and stop the self-re-exciting chains described above.

The results so far obtained do not allow of a complete answer to the questions, but they show clearly that some at least of the more complex capacities of *Sepia* (such as that of following its prey out of the field of view) depend on the integrity of these highest supra-oesophageal centres.

Previous work on behaviour and learning in Cephalopods

In addition to the elaborate organisation of the central nervous system, the Cephalopods possess highly developed sensory and motor systems, and it is generally agreed that they show a complex or 'higher' pattern of behaviour. Unfortunately there has been very little attempt to justify this estimate by detailed observation or classification of the acts of which the animals are capable.

The 'higher' qualities of behaviour may be said to include:—(i) wide sensory and motor capacities, that is to say the ability to respond to varied aspects of the surrounding situation and to make this response in varied ways; (ii) the power to pursue an objective by indirect means, for instance to take a devious route in order to obtain food, or otherwise to show 'intelligence' in the solution of problems; (iii) the possession of conspicuous capacity for learning, *i.e.*, allowing the functional state of the nervous system to change so that present response is modified by past experience.

The wide sensory and motor powers of the Cephalopods are well known and need no further comment. It is with the second and third of the above types of capacity that we are here concerned. There are very few reliable data about the ability of the Cephalopods to obtain their ends by indirect means. Pieron (1909) claimed that Octopods are able to uncork a bottle in order to obtain crabs seen through its glass wall, and similar statements are frequently made in semi-scientific literature. Unfortunately in no one case has sufficient detail or documentation been given to show whether the interpretations applied are correct. The observations detailed below show that *Sepia* is certainly able to follow a prawn which has moved out of its visual field, a by no means simple type of behaviour.

The data about the learning powers of these animals are slightly more satisfactory. Mikhailoff (1920) and Kühn (1930) have shown in Octopods

that formation of simple conditioned reflexes is possible, touch being the unconditioned stimulus used for conditioning coloured lights to produce chromatophore changes or flight reactions. Kühn was able to show that discrimination depending upon both wavelength and intensity is possible. Von Uexkull (1891) claimed that Octopods which have once attempted to eat crabs covered by Sea Anemones not only never do so again but actually refuse all further food. However, this remarkable conditioning is denied by Polimanti (1911).

The capacity to discriminate between visual shapes is highly developed, the eyes being well suited to the purpose (Alexandrowicz, 1927; Heidermanns, 1928). Tinbergen (1939) has recently shown, by studying the responses of *Sepia* to models of the opposite sex, that colour pattern as well as type of movement determines sexual recognition. It is highly probable, though no experiments have been made on the subject, that the prey is recognised by its visible shape.

K. and J. ten Cate (1938) have shown that *Octopus* is able to discriminate between a square and a triangle, or between large and small squares, though it is not clear how far size, rather than shape, was reacted to.

There is evidence, therefore, that changes may take place in the nervous system of Cephalopods which modify subsequent reactions. There appears to have been no previous work aimed at discovering the effects of removal of any part of the CNS on this capacity. Indeed there exist only fragmentary observations on the effect of operations on the CNS on the behaviour of these animals. Bert (1867) using *Sepia* and Fredericq (1878) with Octopods, claim that after removal of the entire supra-oesophageal ganglia the animals become wholly passive and show no further spontaneous movements. This was confirmed for Octopods by Phisalix (1892, 1894) who performed a number of operations on the CNS in connection with a search for the chromatophore centre. His observations were mostly concerned with chromatophore changes following operation, but he noted that superficial supraoesophageal lesions do not affect the movements of the animal, while injury to deeper parts produces considerable motor disturbances. Interpretation of all these observations is made difficult by the absence of histological control to show exactly what was removed. In the present work we have attempted to remove, or to interrupt the functions of, only those centres which, as we have seen above, would be expected to constitute the 'highest' portion of the CNS.

OPERATIVE TECHNIQUE

Operation on the supra oesophageal ganglia of *Sepia* is made difficult mainly by the the profuse bleeding which follows opening of the 'cranium.' The animals are anaesthetised with 2 per cent urethane in which they become immobilized in a few minutes. Anaesthesia should be carried to the point at which all the chromatophores become contracted but the respiratory movements of the valves of the mantle still continue. This point is not easy to judge, and some animals were lost through carrying the anaesthesia to a point at which the respiratory movements stopped. Artificial respiration, either by pressing the mantle with the hand, or by direction of a stream of water over the gills is sometimes effective. The animals were wrapped in a damp cloth during the operation, which must be completed

in about fifteen minutes, unless a period of respiration followed by a second anaesthesia is given. No aseptic precautions were taken, but no serious infection was found.

A longitudinal incision is made in the skin between the eyes, and the 'cranium' exposed by severing the muscles attached to its anterior wall. A transverse cut is then made with a fine blade, low down, through the front wall of the cranium, followed by longitudinal upward cuts such as to free a flap of cartilage which can be held up to expose the supraoesophageal ganglia. Profuse bleeding begins as soon as the cranuim is pierced, and in spite of swabbing it is often necessary to operate in a pool of milky bluish blood. The animal may lose several millilitres, apparently without serious ill effects. The bleeding is due to the unavoidable rupture of the intra-cranial venous sinus, but the arteries for the supra-oesophageal ganglia and optic lobes run up at the sides of the *back* of the cranium, and are not interfered with by this anterior approach.

The superficial lobes of the supra-oesophageal mass can, with practice, be distinguished externally, and incisions can be made into them as required with a fine sharp cornea knife. The lobes with which we are here concerned are the most superficial and can be easily removed. The whole of lobus verticalis can be sliced off without damage to any other centres. By entering lower down, lobus frontalis superior can be removed, with or without verticalis. Closure of the wound is effected by two or three stitches in the skin. In spite of the damage to the venous sinus post-operative bleeding is very slight, and recovery and survival are good.

The effect of the operative procedure itself on the animal was controlled by making incisions into the skin and cartilage and then closing again without damage to the central nervous system. It is essential to control all lesions by histological examination, since their extent can never be properly determined at operation and autopsy, and secondary changes due to interference with blood supply must be looked for. Post-morten changes in the nervous system are very rapid, and all material was therefore taken immediately after the animals had been killed by decapitation. The eyes were removed, and the whole cranium and central nervous system then fixed in a mixture of 15 parts of 40 per cent neutral formaldehyde and 85 parts of sea water. Any attempt to remove the CNS from the head, or to explore the extent of the lesion at autopsy, leads only to uncertainty as to the extent of the true operative damage.

Material can be kept in formol for several months and is then stained with the modified Cajal's method described by Young (1939). The staining, however, should be undertaken as soon as possible, since with lapse of time the connective tissue is found to stain more strongly, and the nerve fibres less strongly. Good nerve stains can be obtained after one year in the fixative, but pieces kept for five years show only connective tissue.

All material was embedded in celloidin and sectioned serially at 50 or 100μ. This procedure well repays the great labour involved, since it gives a very beautiful picture of the fibres in the neuropil, and also often of their connections with the cells. Degenerating tracts can be identified during the first few days after operation by the rows of granules which they contain. Secondary pathological changes such as those produced by infection or anemia are easily recognised.

Experimental Results

Removal of verticalis complex

Absence of motor defects or forced movements. Table 1 shows the extent of the injury, as revealed by serial sections, in the animals chosen for critical study. In order to map the lesion, the total number of sections (usually sagittal, occasionally transverse) occupied by the verticalis was counted, and divided by 5. The sections corresponding to each of 4 points across the hemisphere was then plotted on to a standard outline of the verticalis and frontalis superior. This outline was obtained from a suitable horizontal section, and is not exactly that seen from above, since the upper part of the verticalis overhangs the l. frontalis superior. A standard outline of a sagittal section was then filled in to show the *maximum* depth of the lesion, which of course did not always extend as deeply as this over the whole area.

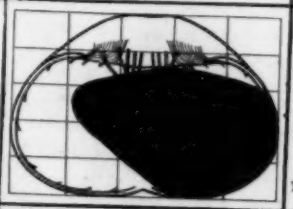
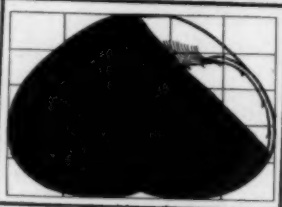
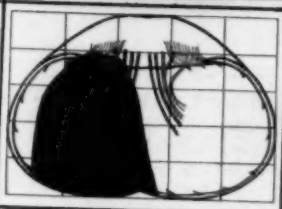
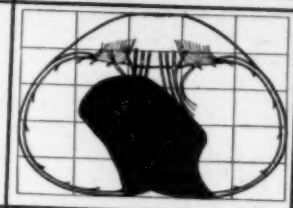
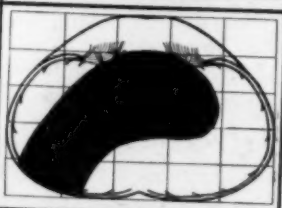
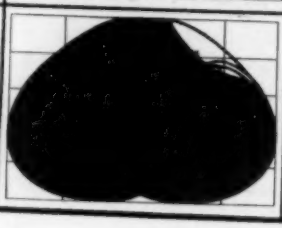
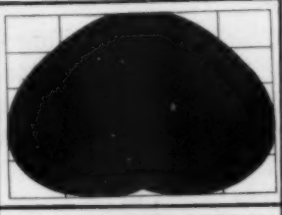
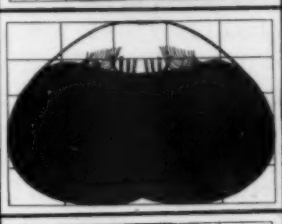
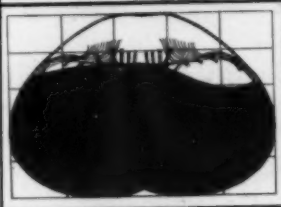
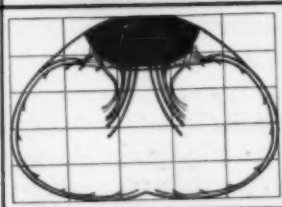
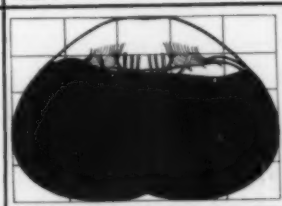
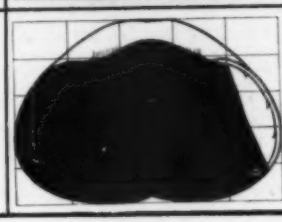
Sepia	Died or Killed	Survival. Days	Surface View of Lesion	Maximum Depth of Lesion
IJ	D	2		
IY	K	3		
LP	K	2		
NQ	K	3		
OA	K	17		
NU	K	2		

Table 1.—Diagrams of supraoesophageal ganglia of Sepia to show the extent of

Sepia	Died or Killed	Survival. Days	Surface View of Lesion	Maximum Depth of Lesion
PA	D	4		
PC	K	9		
PD	K	9		
PE	K	9		
PF	K	6		
PG	D	5		

w th extent of the lesions inflicted. *For method of compilation see p. 503.*

Lesions of lobus verticalis and lobus frontalis superior do not produce any obvious effect on the appearance or behaviour of the animal. After complete removal of either or both lobus verticalis and lobus frontalis superior a *Sepia* swims normally with its funnel or fins, and its colour patterns (Holmes 1940) are unaffected in range or intensity. Moreover the animal can steer its way about the tank, avoiding obstacles, and darting away from an approaching stick without any symptoms of blindness, slowness, or any other disability. There are no clear signs of either increased activity (hyperexcitability) or passivity (depression or hypoexcitability). Without some measure of the activity of the animal such as is provided by cage-running in mice, it is difficult to be positive on such points, but the *Sepia* lend themselves very well to observation in a dimly lit glass-sided tank, and any gross disturbance in this respect would certainly be detectable. Indeed after certain operations on the more basal ganglia there is very marked hyperexcitability, the animal dashing recklessly about the tank after the slightest stimulus, or in other cases moving ceaselessly around: but no one of these symptoms is seen after the removal of the verticalis complex. In fact, *after such an operation the animal is quite indistinguishable in its simple behaviour from a normal Sepia.*

Moreover, after unilateral operations, such as those on animals LP and IJ, in which the verticalis was removed on one side only, *there are no forced movements or circling*, either with the fins or the funnel, though such movements are very pronounced after lesions affecting the more basal supraoesophageal centres, especially lobus basalis anterior (Young unpublished). Nor after such unilateral operation is there manifestation of asymmetrical colour patterns, though these again may be produced by deeper lesions.

Careful search for each of the above symptoms was made in every animal shown in Table 1. There is, therefore, every indication that lobus frontalis superior and lobus verticalis do not directly control any simple motor function, nor supply any tonic excitatory or inhibitory influence whose removal produces gross asymmetry in the animal.

Feeding after removal of verticalis complex. Still more surprising than the absence of motor defects after the removal of these centres is the fact that the animals are able to feed in a perfectly normal manner without them. A normal *Sepia*, when hungry and in the presence of a prawn, goes through a complex and well-marked series of reactions (see Holmes 1940). In the first position, which may be termed *attention*, the arms assume a characteristic posture, the two most dorsal being raised almost vertically and the sickle-shaped fifth pair being held out laterally. Meanwhile, waves of darkening pass over the head, and sometimes also over the body, the upraised tentacles being especially dark.

The next stage may be termed that of *approach*. The *Sepia* swims slowly forward towards the prey, following if the latter moves away. If the prawn moves out of sight at this stage the *Sepia* may follow it around a corner, a reaction which we term *hunting* (see below). As it comes nearer to its prey,

the 'tentacles' begin to protrude from the now forwardly pointing arms, and finally when the prawn is within range the reaction of *seizure* takes place, the long tentacles being shot out and the prey caught by the suckers of the expanded tip or 'hand.'

The whole set of movements is carried out in a 'purposeful' manner, each action being modified by circumstances and not following an invariable course. For instance, if the prawn is placed close to the *Sepia* in a clear space it will be rapidly seized, but if some other moving object is included in the field, or if the prawn is moribund or otherwise atypical, the 'attention' pe-

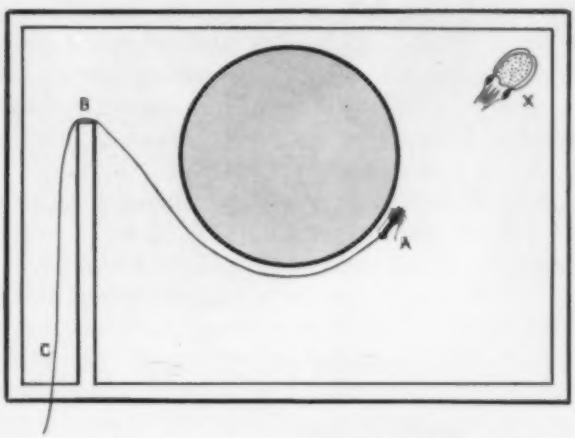


FIG. 4. Arrangement of tank to show capacity of *Sepia* to hunt when its prey passes out of sight, see text.

riod will be prolonged, and the approach very cautious, so that some minutes elapse before seizure is attempted.

After removal of lobus frontalis superior and lobus verticalis, a *Sepia* can attack and eat its prey in a perfectly normal manner, *provided that the food-object remains in the visual field until captured.* When a prawn was placed in the tank, 'attention', 'approach', and 'seizure' were seen to take place in all the animals in Table 1 in a manner indistinguishable from normal, providing that no 'hunting' was required. These centres are therefore not an essential part of the mechanism by which the shape of the food-object is recognised, or the hunger drive operated.

There is, however, some effect of the removal of these centres on feeding, since the animals often refused food for some days immediately after the operation, or, as in the case of animal PE, showed 'attention' but made no attempt at seizure of the food. No such changes were seen after a control procedure in which the cranium was opened but no damage inflicted on the CNS (see Fig. 5).

Inability to hunt after removal of verticalis complex. In order to investigate the capacity of *Sepia* to hunt food which disappears out of its sight, a black

thread was tied to the tail of the prawns, and the tank provided with a simple maze in the form of an enamel plate stretching three quarters of the way across the tank, and an enamel bucket (Fig. 4). The prawn was placed in the tank at A, in such a way that it could be seen by the *Sepia*, which was at rest in the corner at X.

If necessary the *Sepia* was steered to this point before each experiment, but this gave little trouble since nearly all animals chose this corner as a permanent point of rest during the day, always returning to it after excursion round the tank or capture of the prawn at the end of a trial. When the *Sepia* showed 'attention' and began to follow the prawn, the latter was withdrawn out of the visual field behind the bucket and allowed to rest at the corner B. If the *Sepia* followed round the bucket until it could again see the prawn, the latter was further withdrawn behind the enamel plate to C, where the *Sepia*, if it had followed round the corner, was allowed to seize and eat the prey. The presence of the black thread did not appear to interfere with 'attention' or feeding in any way.

The arrangement therefore makes it necessary for the *Sepia* twice to follow its prey after the latter has passed out of its sight, and the experiment thus tests the capacity of the animal to make a response to a situation in which no directly stimulating object is in the visual field. Put in another way it tests whether the animal is able to retain the association of a particular locality with the food-object which is no longer present there, and to use this association for its hunting. A great advantage of this experiment is that it investigates a type of response likely to be of use to the animal in its natural surroundings among the rocks, and is therefore perhaps of greater interest than discovery of the capacity of the animal to discriminate triangles from squares, or to learn the problems discussed later (p. 26).

When tested in this way, a normal *Sepia*, provided it is hungry and has become accustomed to the tank by living in it for a day or so, shows 'attention' as soon as the prawn appears, advances towards it, follows round the bucket and the edge of the plate, and eats it at C. The following is often rapid and the whole reaction accomplished within a minute or less. At other times the animal waits for as much as two minutes before gradually turning the corners. Occasionally, if the prawn is withdrawn very soon after having been placed at A, the *Sepia* does not follow round the bucket, but retreats again to its corner.

If the cuttlefish has been sated it usually gives no sign even of attention, much less of following, or it may give attention without following. The number of prawns which will be taken daily varies considerably; often it is only one, sometimes two or three. A hungry animal which has just finished a prawn will often immediately take another, perhaps even a third, but thereafter shows no further attention to prawns for some hours. If one prawn only is given daily, normal animals give the hunting reaction with complete regularity at each day's presentation.

After removal of lobus verticalis, however, the behaviour is very different. The *Sepia* shows attention to the prawn, and advances towards it, but

when the latter is withdrawn out of sight, *the cuttlefish never hunts it*, even round the edge of the bucket. As will be seen from Fig. 5, this was tested many times on the operated animals. Every device was used to encourage the animals to follow and hunt, the prawn being withdrawn as slowly as was possible without its being captured by the *Sepia*. In every case, however, when the prawn disappeared from its field of view, the *Sepia*, after pausing for few seconds, shot back to its corner as if baffled. The course of the experiment may be shown by a typical case (see Fig. 5), *Sepia OA*. Before operation the animal was given two trials on each of two successive

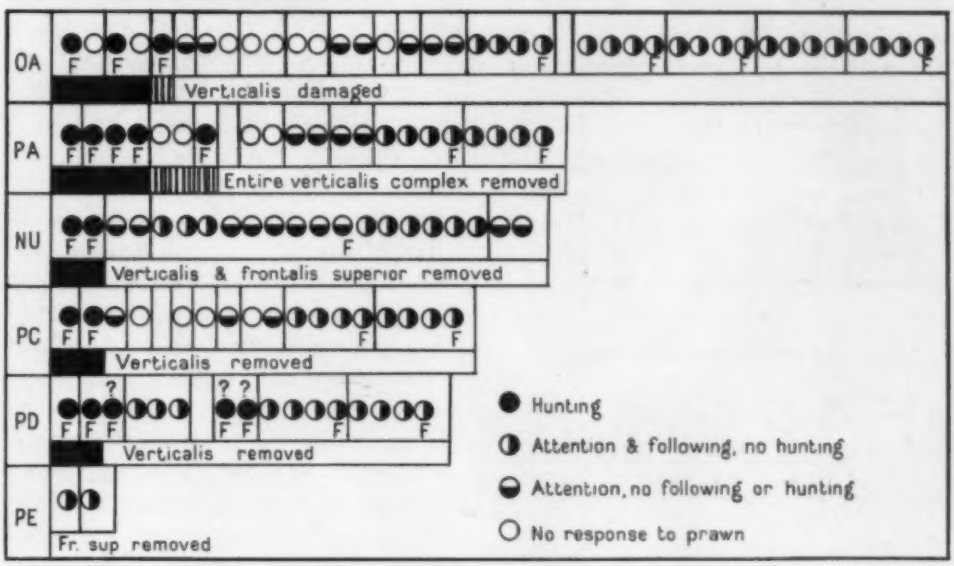


FIG. 5. Failure of *Sepia* to hunt after injury to the verticalis complex. Each spot indicates a test whose result is indicated by the key. The vertical lines indicate days. The black area below each row of spots shows the period before operation of the animal, the vertically hatched area the period after a control operation, and the area with the lettering the period after the operation as named. The *Sepia* was allowed to eat the prawn in the trials marked F, but had no other food throughout the experiment.

days, giving the full hunting reaction on the first trial of each day, but showing no 'attention' at the second trials. On the third day a control operation was made, the skin being incised and the cranium opened, but the wound then closed without any injury to the supra-oesophageal ganglia. After recovery from anaesthesia a further trial was made and a hunting reaction again obtained. On the fourth day the wound was opened again and a lesion made which was presumed to cut off the whole lobus verticalis. For thirteen successive trials during the succeeding 8 days, the animal either took no interest in the prawn, or showed 'attention' without following. Then followed 20 trials during a further 6 days, at each of which there was attention and following of the prawn, but in which the animal was unable to perform the hunting reaction, that is to say to follow when its prey moved out of

sight. The procedure on each of these days was to test the animal 4 times, twice in the morning and twice in the evening, by drawing the prawn away from it, so that each day's performance consists of four tests of the ability of the cuttlefish to hunt. On each day after the four tests, the *Sepia* was allowed to catch and eat a prawn. As will be seen from Table 1, subsequent sections showed that in this animal sufficient of lobus verticalis had been removed to interrupt tractus verticalis-frontalis superior on both sides, though large amounts of the lateral part of verticalis were intact, as was most of frontalis superior.

As will be seen from Fig. 5, essentially similar results were obtained with animals NU, PA and PC when tested in the same way. Two further animals, PD and PE, were tested by a somewhat different, and as it proved less satisfactory, technique, using the tank designed for the learning experiments described in the next section. Each animal was confined in a separate runway (see Fig. 6) one end of which was closed by a sliding wooden door, which when opened revealed the prawn. As the *Sepia* moved up towards the door the prawn was removed sideways out of view, and a positive hunting reaction was recorded when the *Sepia* continued onwards through the doorway. The defect of the device was that the runway was too short, so that if the *Sepia* moved fast it was apt to be carried through by its own momentum. Moreover it was difficult to withdraw the prawn fast enough to take it out of the view of the *Sepia* for more than a short time. In spite of this difficulty the results are included, since animal PD 10 times failed after operation to make the very simple hunting reaction necessary to capture its prey in this device. At three trials it did pass through the doorway, but in each of these cases it came up the runway very fast, and probably kept the prawn in view throughout.

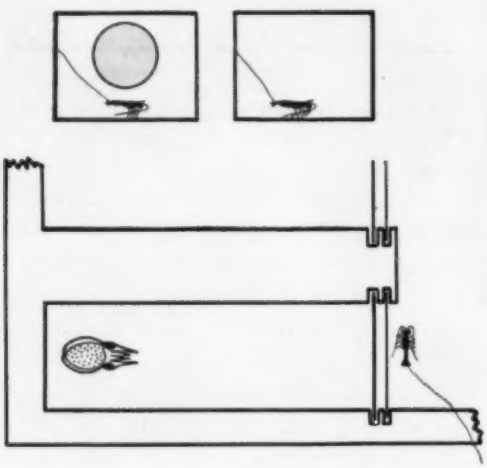


FIG. 6. Arrangement for testing reaction of *Sepia* to a prawn behind glass. Above is shown the end of the tank as it would appear with and without the glass and white spot.

Sepia PE was an animal previously tested and operated in connection with the learning experiments to be described in the next section. Accordingly no record was made of its ability to perform a hunting reaction before operation; however, every normal animal tested proved able to hunt. Tested in the runway *after* operation, it gave 2 successive trials in which attention and following of the moving prawn took place, but without the ability to perform the hunting reaction of coming through the door. These 2 animals,

therefore, provide further confirmation of the result shown by the other four, namely that following of food which has been moved out of sight is not possible after injury to the verticalis complex.

Experiments on learning in Sepia

A further series of experiments was designed to study the modification of behaviour as a result of experience, and the relation of this power to the verticalis complex.

Inhibition of 'seizure' reaction. It was noticed that if a glass jar containing a prawn was placed in a tank of *Sepia*, the animals at first attempted to seize the prawn, shooting their tentacles repeatedly against the glass. Gradually the attacks became less frequent, and finally the prawn was completely ignored. Clearly some change takes place in the nervous system such that a situation which at first elicits the attacks on the prawn later fails to do so. This inhibition of feeding reaction was further studied by keeping the animals in a tank provided with running seawater, divided by means of longitudinal partitions into a number of runways, each closed by a sliding wooden door (Fig. 6). One animal was confined in each runway for the duration of the experiment. The opening of the wooden door gave the animal access to an open space in the tank. In addition, slots were provided at the open end of each runway, so that a sheet of glass, as well as the wooden door, could be placed across the opening.

The animals were placed in the runways and allowed several hours in order to become used to the tank. At the beginning of an experiment the glass plate was placed in position across the end of the runway with a prawn behind it, the wooden door being kept closed. The door was then opened and the *Sepia* in the runway allowed to attempt to take the prawn, which it did repeatedly, shooting its tentacles violently against the glass plate.

It was found in the course of an experiment that this ejection of the tentacles became less frequent. The frequency of ejection was thus used as an index of the state of the animal, and, taking zero as the time of opening the door, the time (in seconds) at which each 'shot' was made was recorded. The experiment was ended when 3 minutes passed without any shot being made. The animal was then left undisturbed in the tank for a number of hours and then tested again with the same technique, the time of each shot being again taken until none had occurred in 3 min.

The animals were not fed throughout the experiment, which lasted at the most for ten days. They are able to starve for such long periods without showing obvious debility. In order to follow quantitatively the change which is occurring in the state of the nervous system as the learning proceeds, the number of shots per two minutes was plotted against time as shown in Fig. 7. With each of the animals tested it was found that the rate of tentacle ejection fell off from a very high value at the beginning of the first test period, until after 20–30 min. the criterion of no shots per 3 min. was reached. The curve is not smooth, but shows several minor peaks.

When the test was repeated after intervals up to eighteen hours, the animals usually made some shots at the glass, but *always less than in the first experiment*. The highest frequency of shots was often reached some minutes after the beginning of the test, and thereafter rapidly declined, the 3-minute criterion being reached much sooner than in the original test. Moreover the time taken to reach this criterion tended to become shorter at each successive test, the fall in this value showing a more or less regular 'learning curve.' Thus not only does the state of the nervous system change during the course of one test: the animal 'learns' to inhibit its seizure reaction: but also this

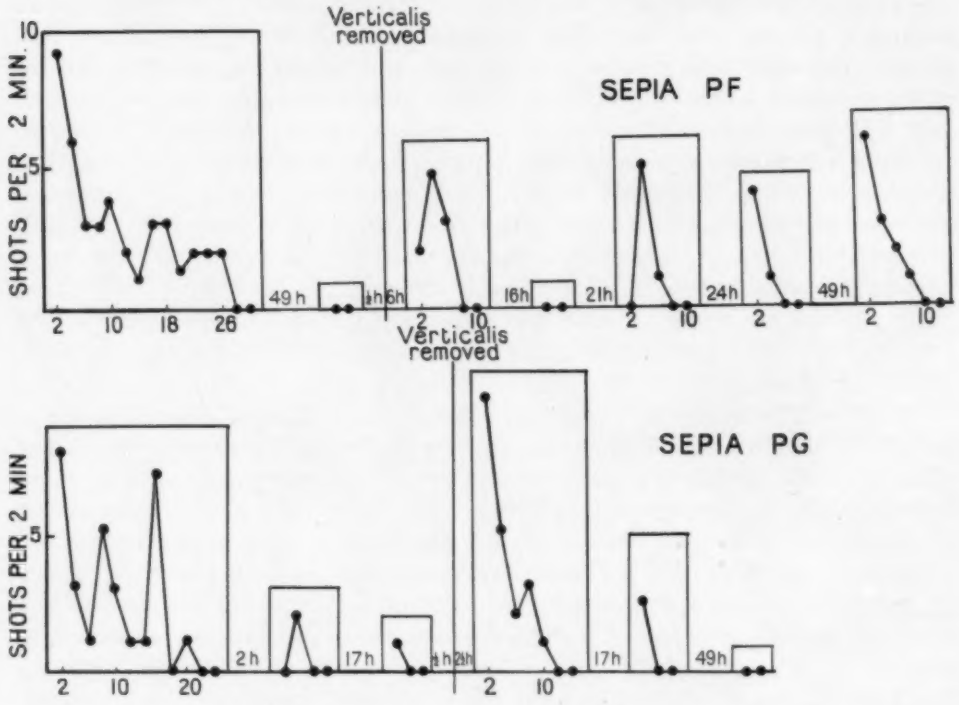


FIG. 7. Graphs showing the number of shots made at the glass per 2 min., before and after injury to the verticalis complex. The time scale for each test is in minutes and the periods between the tests are given in hours.

learning is carried over a period of at least 18 hours. But in most cases the change of state in the CNS, whatever it may be, which enforces this inhibition is partly reversed after such an interval. The animals have partly 'forgotten,' but quickly learn again.

Details of the maximum period of retention were not further investigated since the purpose of the experiment was to test the effect of the removal of the verticalis complex upon learning. The results are not wholly consistent. Sepia PG showed the clearest result. When tested after the operation it showed a higher frequency of tentacle ejection than at the very first test.

This is very remarkable since only 3 hours elapsed between this test and the last before operation, whereas the inhibition was not lost in the much longer periods between the pre-operational tests. There can be no doubt that the operation has produced a marked effect on the learning. However, the experiment is uncontrolled since the effect of anaesthesia alone on the learning was not investigated. Much more significant is the fact that after this initial high value the ejection frequency fell off sharply. Therefore, even after an operation in which, as Table 1 shows, very nearly the whole of the lobus verticalis had been removed, the animal was able to learn to inhibit the seizure reaction. Moreover it learns to do so more rapidly than in the first test, that is to say some part of the changed state of the CNS is carried over in spite of the operation. It is therefore quite clear that the change of state involved in this particular act of learning does not occur only in the verticalis complex.

Sepia PF showed similar behaviour in that considerable traces of the

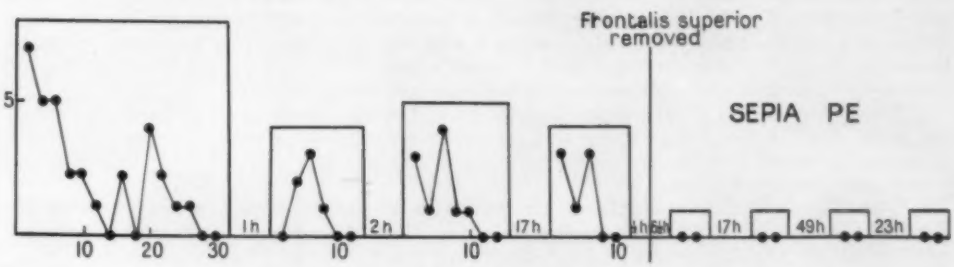


FIG. 8. As for Fig. 7. In this case the *Sepia* made no further shots at the glass after operation.

learning persisted over the operation, without, however any very high post-operative frequency of tentacle ejection.

Sepia PE gave a most curious result in that during five post-operational tests it at no time shot its tentacles at the glass. At each test the *Sepia* showed attention to the prawn throughout the experimental period, thrusting its head against the glass and moving excitedly up and down the tank, but never once were the tentacles ejected. In this case the operation, far from causing the animal to forget the learned inhibition, appeared to have made this inhibition more profound. It will be remembered that in the experiments detailed on p. 509, the feeding reactions were often affected during the period immediately after operation. But in these cases attention to the prawn was rare, whereas here there is clear evidence of attention, but a curiously accentuated inhibition of seizure. The operation performed in this case was the removal of lobus frontalis superior, not verticalis itself. It acts as a warning against treating all lesions of the verticalis complex as if they were equivalent, but in the absence of further evidence it is impossible at present to pursue further the questions which it raises.

In spite of the differences between the behaviour of these 3 animals, they

agree in showing that the change of state involved in learning to inhibit the ejection of the tentacles does not occur in the verticalis complex, since considerable traces of the learned state may persist after removal of this complex, and subsequent learning is at least as rapid as that before removal. The experiments indicate however that the verticalis complex may have some influence on the type of learning studied even though its presence is not necessary for the learning to take place.

Discrimination. The reaction of tentacle ejection was also used in a study of the ability of *Sepia* to learn a discrimination problem. The animals were presented with a prawn behind a glass plate marked with a white circle, and then learned not to eject the tentacles at this, while continuing normal ejection at a prawn presented without a glass plate. The discrimination was thus between 'prawn' as a food-object, and 'prawn plus white circle' as a non-food-object.

Apparatus and technique. The apparatus used in this experiment was a wooden tank divided into runways as in the case of the tank used in the study of tentacle ejection inhibition alone (Fig. 6). As the discrimination presents a much harder problem for the *Sepia* than the reactions previously described, and the experiment was consequently much longer, each runway was provided with a separate sea-water supply, and the animals kept permanently in this space for several weeks remained very healthy.

Every day each animal was given a group of 4 trials. These trials were of two types: (i) *'glass' trials* in which the prawn was presented behind a glass plate bearing just above its centre a painted white circle two inches in diameter; (ii) *'feeding' trials* in which the prawn was presented alone.

The technique of presentation of the prawn in the case of both types of trial was the same as that described for the experiments above. The daily group of trials was made up as follows: (i) *Three* successive 'glass' trials; (ii) *The fourth* and last trial of the day, a 'feeding' trial, in which no glass was used, and the *Sepia* allowed to reach and seize the prawn.

This grouping of trials was evolved to meet a practical difficulty, that of giving a number of trials on the same day. In the normal manner, an animal being trained in a discrimination problem would be given a number of trials of the two different types (*e.g.* in this case 'glass' and 'feeding' trials) arranged in a purely random order. However it was found in preliminary experiments that it was undesirable to feed the *Sepia* with more than one prawn a day. Thus if a 'feeding' trial preceded a 'glass' trial on any one day, the *Sepia* was unlikely to take any interest in the prawn at the second trial. A random arrangement of 'feeding' and 'glass' trials would thus limit the experiment to one trial per day. An alternate arrangement of 'glass' and 'feeding' trials was avoided, since it might possibly be objected that the animal was learning to respond to very alternate trial rather than to 'prawn' versus 'prawn+white circle'. As it is very unlikely that the CNS of *Sepia* would enable discrimination of every 4th trial from the rest, solely by virtue of its position in the series, the above arrangement was adopted. This gave the convenience of 4 trials per day, combined with the advantage of not feeding the animal until the last trial of the day.

In the case of 'glass' trials two indices of the state of the animal were taken, the time in seconds from the opening of the wooden door to the first

ejection of the tentacles, and the number of shots made in the first two minutes following this first shot. It was found that the time to the first shot lengthened and the number of shots made in the extra period declined during the course of the experiment. The discrimination was regarded as learnt when in each of the 6 consecutive 'glass' trials (*i.e.*, the trials of 2 successive days) no ejection was made in the first five minutes of experiment, while in the 2 accompanying 'feeding' trials positive responses (*i.e.*, feeding) were recorded. The number of shots made at the glass each day during the 2 min. is thus an index of the extent to which learning has taken place. When plotted against time the number of shots declines with the irregularity typical of most learning curves. When the total number of shots in three successive days of experiment are plotted, the general slopes of the curves appear, and are seen to be similar for the three animals investigated (Fig. 9).

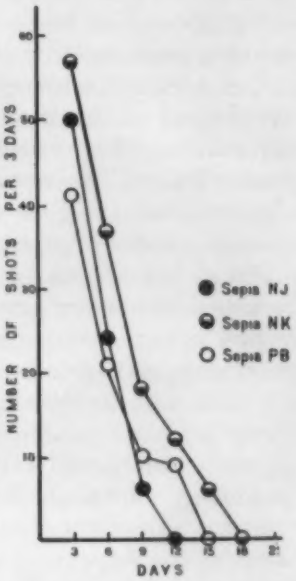


FIG. 9. Graph of course of learning not to shoot at prawn behind a glass plate on which there is a white circle. The ordinate shows the number of shots made at the glass (*i.e.*, 'mistakes') during successive periods of 3 days.

Figure 10 is a diagram illustrating the progressive changes in the behaviour of the three animals during the course of this learning. At the beginning of the experiment 'glass' trials were invariably accompanied by shooting, but quite early, with all three animals, there appeared occasional trials in which there was attention or approach to the glass without any tentacle ejection. As the experiment proceeded, such trials, involving only attention or approach, grew more frequent, as did trials in which the *Sepia* ignored the prawn entirely, though continuing to seize the prawn in the accompanying 'feeding' trials. Finally, the criterion of learning adopted was reached. All 3 animals proved capable,

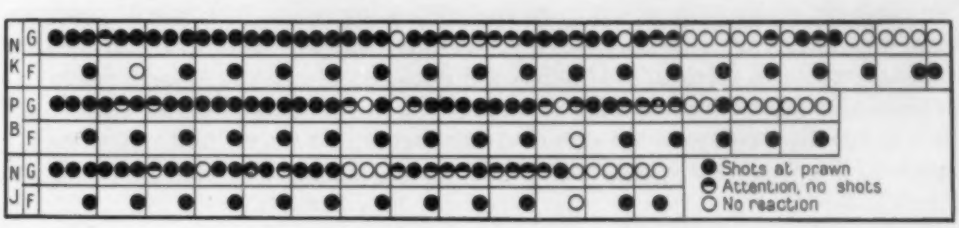


FIG. 10. Diagram to show the gradual failure of *Sepia* to respond to a prawn shown behind a glass plate provided with a white circle. For each animal the upper row of spots (G) shows the 'glass' trials and the lower row (F) the 'feeding' trials, there being three of the former and one of the latter daily. Vertical lines mark the days. During the experiment each animal gives progressively fewer trials at which there is attention or shooting if the white circle is showing, while continuing to shoot when it is absent.

therefore, of making a discrimination between 'prawn' and 'prawn+white circle' as objects of different significance. The criterion adopted was reached in the case of Sepia NJ after 38 'glass' trials, and in the cases of NK and PB, after 55 and 48 trials respectively. The discrimination is of a similar sort to that performed by the 2 *Octopus* of K. and J. ten Cate (1938).

A question arises concerning the importance of tactile influences in the setting up of this discrimination. In some of the trials in which there was attention and approach but no seizure, the animal 'felt' the glass with its tentacles, and of course, during the abortive shooting of the tentacles in 'glass' trials, the glass was struck violently by the ejected tentacles, so that tactile, possibly 'painful', stimulation must have been involved. Whatever tactual stimuli are involved in the learning, when the final criterion was reached, the *Sepia* remained immobile at the end of their tanks in the trials when 'prawn+white circle' was presented, a situation in which the *Sepia* has of course, no tactual relation with the glass plate.

The only further difference, other than optical, between the two situations in which positive and negative responses were given, is that in the 'glass' trials possible chemical influences emanating from the prawn are excluded. Although chemoreceptors are certainly present in Cephalopods, there is no evidence that they function as distance receptors. Indeed the fact that at the beginning of the experiment the *Sepia does attack* the prawn in 'glass' trials shows that the distance receptors involved are the eyes. Thus there is every reason to believe that *Sepia* can make a discrimination between the two visual situations.

Unfortunately the experiments were interrupted before we could make tests of the retention of this type of learning or of the effect upon it of the removal of the verticalis complex. However these experiments show for the first time that *Sepia* is capable of learning to make such a discrimination, and indeed that it lends itself well to this type of experiment.

Discussion

From all of these experiments it is clear that changes of state may occur in the nervous system of *Sepia*, so that following certain situations the reaction capacities are altered. After a prawn has disappeared round a corner that corner exerts an attraction which it did not possess before. After a *Sepia* has repeatedly and vainly shot its tentacles at a prawn behind a glass plate, the futile reaction ceases to be given. After training, a *Sepia* will not attack a prawn if a white circle is also present, but only when the prawn alone appears.

Such modifications of behaviour are all examples of a process which may be called learning, and they show capacities which are likely to be extremely valuable to the animals in meeting their daily needs. This is especially clear in the case of the hunting reaction. A search for prawns among rocks would be difficult for a *Sepia* which was unable to follow its prey out of sight. The other situations studied, though they are never likely to be met with in the

life of the animal in this form, yet show capacities for modification by experience which could be applied to many situations.

These experiments, then, give us further knowledge about the behaviour and mode of life of the cuttlefish. But the main purpose of the investigation was to attempt to discover something of the nature of the change which takes place in the nervous system during the process of learning. All hypotheses hitherto suggested about this change have proved either inadequate to cover the facts or inacceptable to the physiologist (see Lashley, 1934, for summary). The particular hypothesis upon which the present work has been based was that the change taking place during learning consists in the setting-up of self-re-exciting activities which so facilitate the effects of impulses from sensory sources as to make them able to produce a response which they could not elicit before the training. Such a theory certainly allows us to understand some of the aspects of learning. For instance, once the activities have been set up, they might well affect large masses of nervous tissue, so that facilitation would be available for impulses from sources other than the peripheral receptors originally used in learning. Similarly, the degree or amount of learning, as expressed by the learning curve, would depend upon the number of neurons activated in a particular cyclical manner, and when large numbers are set in action at once, sudden drops in the learning curve, 'insight solutions' and the like are produced. Further, a possible basis is provided for the observation that the rate of learning depends on the quantity of tissue present (Lashley 1934 atc.).

In its present form, however, the theory does not give a clear view of the mechanism 'by which a response to a ratio of intensities is brought about' (Lashley, 1937). Thus during the present investigation it has been shown that there is some mechanism in the optic lobes by which a *Sepia* reacts to a prawn as a food-object, or by which the reaction of ejection is inhibited when the prawn is behind a glass plate. The element in these or any other discrimination reactions which is so difficult to understand is that they depend on giving a particular set of reactions to specific patterns of excitation received *anywhere* on the sensory surface. Thus we have to imagine that at least a large portion of the optic lobe is able to elicit a feeding reaction whenever the prawn shape is represented in it, even though individual elements are very variously stimulated at successive presentations.

The only contribution we can bring to this problem is the demonstration that discrimination of this type can certainly be performed in the optic lobes of *Sepia*, without the participation of the verticalis complex. After removal of the latter the cuttlefish not only still shows specific reactions to food-objects, but is able to reverse this discrimination, learning to inhibit the ejection of the tentacles at a prawn behind a glass plate.

However, it seems that the power to form the association involved in the hunting reaction is dependent on the integrity of the verticalis complex, and it is reasonable to suppose that this effect depends in some way on the reactivation of the optic lobes through the cyclical pathways shown in Fig. 1.

Thus it may be that the presence of the food object, in addition to eliciting the feeding reaction, also sets up processes in the verticalis complex which so influence the optic lobes as to cause associated configurations, such as the corner round which the prawn has disappeared to elicit following reactions which they alone could not produce. Since we know nothing of the method by which one configuration rather than another produces its effect it is not profitable at present to speculate further on this baffling theme.

The hypothesis of self-re-exciting chains, in the simple form of the interaction of lobes considered above, is clearly inadequate to meet all the requirements of learning situations even as simple as those here studied, which demand a knowledge of how masses of tissue, such as the optic lobes, change their state so as to become responsive to certain configurations projected upon them. It is by no means excluded that self-re-exciting activities within the lobes play a central part in such changes. For further advance we require more information about the structure and mode of activity of the centres in which such changes take place. There is everything to be gained from study of these centres in as many animal types as possible.

The present study has at least shown something of the capacities of *Sepia* and of the activities of its higher nervous centres. Perhaps the most outstanding point is that removal of the verticalis complex not only does not produce any gross motor abnormality but does not even prevent discrimination, or feeding, though it may affect these processes indirectly, and certainly makes the hunting reaction impossible. The optic lobes alone, as we have come to realise ever more fully as the investigation proceeded, are able, with their relatively uniform, if complex, structure to mediate by themselves many of the more elaborate types of behaviour.

Summary

1. Four types of centre are recognised in the CNS of *Sepia*, (a) *lower motor centres*, in the sub-oesophageal ganglia, comparable to the spinal cord of mammals; (b) *higher motor centres* at the base of the supra-oesophageal ganglia; (c) *primary sensory centres*, such as the optic lobes, and (d) *correlation centres*, occupying the dorsal region of the supra-oesophageal ganglia.

2. The correlation centres, the verticalis complex, allow opportunity for interaction between impulses from various afferent sources, and send tracts to the higher motor centres and to the optic lobes.

3. Faradic stimulation of the lobes of the verticalis complex produces no visible movements; they are 'silent areas.'

4. After complete removal of the verticalis complex the behaviour of a *Sepia* shows no superficial abnormalities. The animal is not blind and can steer and move around as if normal. There is no evidence of either hyperexcitability or depression.

5. After unilateral removal of these centres there are no forced or circling movements, or colour asymmetries, though such are found after injuries affecting the more basal centres of the supra-oesophageal ganglia.

6. After complete removal of the verticalis complex a *Sepia* shows the reaction of attention to a prawn and advances towards it, seizes it and eats it in a manner indistinguishable from normal.

7. A normal *Sepia* is able to hunt, that is to continue to follow a prawn which passes out of its sight round a corner.

8. After removal of the verticalis complex *Sepia* is unable to hunt in this manner, and can then catch its prey only if the latter remains within the visual field.

9. If a normal *Sepia* is presented with a prawn behind a sheet of glass it will shoot its tentacles at the glass, but with a frequency which steadily diminishes. When tested after intervals as long as eighteen hours, considerable traces of this changed state are still evident, the tentacles not being shot as frequently as in the first test, and complete inhibition being more rapidly reached.

10. Removal of the verticalis complex disturbs this state of learned inhibition in various ways, but distinct traces of a previously learned inhibition are seen after removal, and relearning continues to be at least as rapid as the initial learning. The change of state concerned in this learned inhibition does not therefore necessarily involve the presence of the verticalis complex.

11. Three *Sepia* were trained not to eject the tentacles at a prawn showing behind a glass plate on which a white circle was painted, while continuing to shoot at prawns not accompanied by glass and circle.

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CONVERSION OF PHASIC INTO TONIC MOVEMENTS BY PYRAMID LESIONS[1]

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INTRODUCTION

IN A PREVIOUS REPORT (Smith, Mettler and Culler, 1940) evidence was presented tending to show that the phasic response which is characteristically obtained by cortical stimulation depends, for its clonic factor, upon the integrity of the kinesthetic pathway of the region involved. It was further indicated that, while the primary locus at which the kinesthetic impulses influence the descending flow is at the spinal level, another pathway in the region of the ventral spinocerebellar tract is to some extent involved.

The importance of an investigation into the character and factors concerned in the production of a cortically induced movement need not be here emphasized but it should be pointed out that our particular interest in such movements resulted from the observation that they are altered by extrapyramidal stimulation (Mettler, Ades, Lipman and Culler, 1939). Such movements may be inhibited through the caudate, "held" by pallidal stimulation and also influenced by subthalamic and nigral stimulation. If the movement under investigation, however, is itself a complex it is desirable to resolve it into the simplest elements possible. The present investigation was designed to (i) check the previous results reported by Smith, Mettler and Culler and (ii) discover if the cortically induced phasic movement could be converted into a tonic movement by any procedure other than those previously reported.

PROCEDURE

In our earlier experiments "adult cats were anaesthetized with ether and the cerebral cortex of both hemispheres exposed. The animals were supported in a horizontal position with the legs hanging freely. The motor area was stimulated by using an inductorium and a bipolar silver electrode (2 mm. separation). The depth of anaesthesia and the strength of stimulus were adjusted until a continuous application of the stimulating electrode gave rise to a phasic response." This procedure was also followed in the succeeding experiments excepting where different circumstances are noted and with the exception that a half-rectified 60-cycle stimulator was exployed in place of the inductorium in all cases but those specifically noted below.

EXPERIMENTAL DATA

1. Extension of previous results

In our previous experiments when the dorsal roots from and including C5–Th1 were cut cortical stimulation invariably produced tonic instead of phasic movements.

a. Chronic deafferentiation: A possible objection to this result may be made because the experiments reported were of an acute rather than chronic nature. In spite of the fact that we previously presented reasons for considering cord trauma a negligible factor, 7

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animals were prepared under sterile precautions and the dorsal roots from and including C5–Th1 were cut by the intradural route on one side. Each of these animals was examined one day later. Three did not move the deafferented limbs in spontaneous struggling and in righting themselves, four did. When the cortex was exposed, the three former were paralytic in the deafferented leg while the four latter responded by tonic flexion of this limb, no phasic movements being elicitable.

It is possible that the intradural route may be considered an objectionable one. In order to obviate any possibility of intradural damage four cats were now operated extradurally. The left dorsal roots of nerves C5–Th1 inclusive were exposed, under sterile precautions, in the corresponding intervertebral foramina. After 3 days the cortex of one of the animals was exposed bilaterally and stimulated. Movements of the right forelimb were phasic as usual but only tonic movements could be elicited from the left forelimb. The cortical point having the lowest threshold for this response was the lateral portion of the anterior sigmoid gyrus. The remaining 3 cats were tested on the 4th, 5th and 6th days respectively. Only tonic responses could be evoked from the deafferented limbs. No animals were allowed to run longer than this time since it was concluded that little would be gained by a longer postoperative interval and that regeneration might complicate the results. None of the animals showed any infection and all were moving about on the 3rd day. Examination of the 3 animals allowed to run 4 days or longer showed, at that time, that while they were anesthetic in the limb concerned they could still move it. In walking about (upon the 3 good legs) the anesthetic limb was phasically waved in a semiflexed position. The movements corresponded in a general way with the locomotor pattern. There was little evidence of strength in these vague gesturings. Clonic activity was also manifested in the deafferented limbs during deliberately provoked epileptic seizures and, after the opposite leg had also been deafferented (intradurally), epileptic seizures evoked from the forelimb area still spread to the hind limbs of the animals.

b. Devascularization. In cutting the dorsal roots, by any approach, there is always a certain amount of interference with the vascular supply of the cord. Usually one or two large vessels lying in association with the dorsal root fibers at one specific level are more significant than any or all of the others. By the intradural route such significant vessels may be identified and avoided. We did not therefore consider vascular disturbance to be a significant factor especially since a single lesion applied to the side of the cord, in the region of the ventral spinocerebellar tract, and which involved no widespread vascular disturbance could also convert a phasic into a tonic movement. More positive proof is, however, needed before it may be concluded that interference with the vessels accompanying the dorsal roots is not the agent responsible for the results here reported.

In order to test the vascular factor five animals were prepared by exposure of the cord segments concerned and the dorsal roots from and including C5–Th1 were cut on the left. An ultropak with a light green filter was now swung over the right side of the cord and the vessels of the dorsal roots of C5–Th1 were separated from the nerve filaments and severed. The first animal was found to be paralysed after this procedure. In the second and fifth the movements, after a preliminary period in which only tonic responses occurred, became phasic but it was found, after despatching the animals, that a few small vessels had escaped section. In the third and fourth animals no intact vessels could be found travelling over the dorsal roots concerned.

Immediately after cutting the vessels, stimulation of the left cortex of both of these animals gave tonic and not phasic responses. After the lapse of some minutes phasic movements were elicitable. We cannot find any figures in our records on the precise length of time the tonic activity persisted but our recollection is that it was in the neighborhood of five minutes. This would seem to imply that the tonic stage was not so much the result of anemia as of excessive handling of the dorsal roots and mechanical damage (suction had to be repeatedly used to clear the operative field). The point has, however, no direct bearing upon the main issue which is that phasic activity is elicitable after the vessels entering over the dorsal roots of C5-Th1 inclusive have been severed bilaterally, a much more serious vascular interference than was present in any of our regular experimental animals.

c. Section of spinocerebellar tracts in chronic animal. Following our initial communication in which we reported abolition of phasic activity by lesion in the region of the ventral spinocerebellar tract the question was repeatedly

raised as to whether or not the effect might not be due to interference with a descending instead of ascending tract. To this disturbing criticism we opposed the following line of reasoning: (i) abolition of incoming sensory impulses is sufficient to convert a phasic into a tonic movement and it is unreasonable to assume a separate mechanism to be responsible in cases in which the lesion is more centrally placed; (ii) histologically verified lateral column lesions when not apparently encroaching upon deep tracts were sufficient to convert phasic into tonic activity and (iii) when a lesion could be found which obviously encroached upon deeper tracts it always came from an animal which had been paralysed by the lesion. We were finally forced to admit that this evidence was only of a presumptive nature and set about to gather more conclusive data.

Our first efforts were directed toward an attempt to cut or fulgurate the ventral spinocerebellar tract at the level of the decussation of the pyramids in order to eliminate one of the two main descending tracts from consideration. We were never able to devise a technique which was satisfactory for the approach. All animals in which the spinocerebellar tracts were cut succumbed before they could be satisfactorily stimulated. In some cases they could be kept alive by artificial aids but the cortex was thoroughly unreliable.

Attempts to solve the question by Marchi study also failed to give reliable results. In order to place a cord lesion correctly it is necessary to expose the cortex for stimulation so that the conversion from a phasic to a tonic response can be verified. Such a procedure cannot be carried out without obtaining a certain amount of pyramidal degeneration originating in the motor cortex and thus the purpose of the experiment is vitiated. Besides the cord itself undergoes extension of the original lesion and fibrosis which may produce paralysis and a variety of complications difficult to evaluate. It became apparent that the problem would have to be approached by an entirely different technique.

2. Other procedures designed to convert a cortically induced phasic into a tonic movement

a. Cerebellar ablation, section of the brachium conjunctivum and lesions of the cerebellar nuclei. If the conversion of a phasic into a tonic movement be truly the result of spinocerebellar section then, presumably, removal of the cerebellum might be expected to produce a similar result.

In accordance with this hypothesis 7 cats and 1 dog were subjected to complete cerebellar ablation. By the use of the ligature and suction technique checked by intracranial illumination this is a relatively simple operation and can be rapidly performed with very good results. None of these animals gave any evidence of tonic conversion. Upon cortical stimulation all responded with loose, flabby, rapid, phasic forelimb movement.

It might be objected that total removal of the cerebellum is not a reliable test of the original hypothesis because it is perfectly conceivable that an internal imbalance in the cerebellum may be the factor responsible for converting a phasic into a tonic movement. Were this so removal of the cerebellum from an animal in which the phasic response had already been converted into a tonic one, should reestablish phasic activity. This, however, does not occur.

One cat was prepared by dorsal root section and six by lesion in the region of the ventral spinocerebellar tract at the 4th cervical segment. In each case the movements continued tonic after cerebellar ablation. In 4 of the last 6 cases the movements were

notably changed in character (following cerebellar ablation) in that there was a distinctly tremorous element in the tonic movement and it was not so well nor so long sustained as previously. Neither were the movements of the cats in which the spinocerebellar region had been previously fulgurated of the loose type usually seen following simple cerebellar ablation alone.

It remains to be seen what results are obtained by smaller more selective lesions of the cerebellum and what can be gained by fulgurating the cerebellar nuclei or cutting the two upper brachia. In the following experiments the lesions of the brachium pontis were made by a direct visual approach through the basioccipital and basisphenoid following resection of the larynx, esophagus and prevertebral muscles. Although this sounds like a formidable operation it is really quite simple and almost completely bloodless if done with reasonable care. The removal of cerebellar cortex was also done by the direct visual approach (dorsal, of course) while the deep lesions were made by means of a unipolar tungsten electrode carried in the cerebellar attachment of a Horsley-Clarke instrument.

In 2 animals the brachium conjunctivum was fulgurated on one side. This did not abolish phasic movements on either side. In another, the decussation of the brachia conjunctiva was thoroughly fulgurated. Following this procedure the animal developed a position of antigravity rigidity. In spite of the extreme extensor hypertonia of the forelimbs cortical stimulation of either side still evoked phasic movements. It was, however, noticed that stimulation of the medial side of the anterior sigmoid gyri was more effective than that of the lateral side. Another animal which showed such antigravity rigidity had a more orally placed lesion which fulgurated the decussation of the rubrospinal tracts and, in part, also the red nuclei themselves. Here, too, phasic movements were elicitable but the foreleg was never brought farther forward than a vertical line dropped through the scapulo-humeral joint. Our notes on this case state that "phasic movements of the . . . leg seem to illustrate that it is impossible for the flexors to be operated. In other words the limb seems to be habitually held in a position in which the muscles on the anterior side of the leg are all paralytic and those on the posterior side are tonically contracted. When the cortex is stimulated these extensors seem to be capable of contraction and relaxation [in the production of a phasic movement which occurs entirely posterior to the line of the vertical position]. If the limb is deliberately placed in front of this vertical position it becomes extremely tonic but behind this position it is rather loose."

Removal of the anterior (1 cat) and posterior halves (1 cat), either lateral lobe (2 cats and one dog) or of the vermis and roof nuclei (1 cat) of the cerebellum did not convert phasic into tonic movements. It may be worth noting that, in the latter case, the forelimb movements were decidedly hypertonic. When the lateral lobes were subsequently removed from this cat a typical loose, acerebellar, phasic movement resulted. In another animal in which the globose and emboliform nuclei were both fulgurated, on the right side, there was produced flexor hypertonia on the left and extensor hypertonia on the right. The left leg also developed an athetoid quality. Phasic movements were still elicitable from both cerebral cortices. Fulguration of both nuclei fastigii in another animal produced no such result and did not convert phasic into tonic movements nor did fulguration of the nucleus dentatus in still another animal. In several other animals in which perfect "hits" were not obtained but in which the fulguration approximated the above situations similar results were observed (no effect from the region of the nuclei fastigii and dentatus but motor deformation from the region of the globose and emboliform nuclei.)

The supposition that the inhibitory effect of the cortex is mediated through the cerebropontine fibers and exerted upon the cerebellum has often been advanced. Evidence both in favor and against this theory has appeared. While it would seem unlikely that this system could have been involved in our original experiments it was decided to place a series of lesions

in the brachium pontis to investigate the possibility of conversion of phasic movements into tonic activity by this means.

The pons was accordingly, in one cat, severed in the midline. Following this procedure stimulation of either cortex still gave good phasic movements which presented little difference from those usually obtained except that, as the leg reached the position of full extension, a peculiar spring-like quality was noticed in it. The animal showed a rather greater degree of spontaneous activity than is usual but this was of an orderly and slow type and manifested itself in the appearance of a pattern of "walking." There may have been some accentuation of extensor hypertonia and a rather well-marked "magnet" reaction appeared in both forelegs.

Since unanimity of opinion upon the total crossing of the pontine fibers has not been reached and since it is possible that some opposition between the two sides of the middle brachium exists it was decided to sever the lateral side of the pons. None of these attempts were completely satisfactory, some involved extraneous systems and none were complete. It was subsequently found that the pons could be eliminated as a responsible factor by another process so this method of approach was discontinued. In no case did we obtain tonic movements from these experiments; in many cases the movements which were obtained were very tremorous though not of a typical acerebellar type and in many the threshold of cortical excitability was found to be remarkably reduced after unilateral section of the pons arm. After-discharge was frequently encountered.

While the exact significance of some of the above results is not entirely clear it seems certain that there is little evidence in favor of our original assumption that spinocerebellar tract injury is the responsible factor in the conversion of cortically induced phasic movements to those of tonic type. We may also question the importance of rubrospinal injury in this connection. The problem now arises as to whether, if the brain be entirely disconnected from the cord with the exception of the corticospinal tracts, phasic movement is possible.

b. The role of the corticospinal tract. In order to answer the question just raised the following experiments were performed.

In one cat a ligature was dropped in front of the tentorium in such a way as to disconnect all the neural tissue dorsal to the cerebral peduncles. A certain amount of antigravity rigidity developed but phasic movements were elicitable as usual. Since in this case the corticopontine and possibly corticorubral fibers may have still been operative we prepared a second experiment in which we were successful in producing one animal. In this case the cerebellum and quadrigeminal plate were ablated. The tissue dorsal to and between the pyramids, in the region of the mesencephalon, was now removed. This included the red nuclei. The right peduncle was injured but stimulation of the left cortex still gave phasic movements in the right foreleg. There was still, in this case, considerable tissue left in the pontine region which might conceivably have been eliminated. In order to get rid of this a third experiment was devised in which we were able to keep one cat alive and in good self-sustaining condition. The pyramids were exposed by the ventral approach and a ligature was placed dorsal to them entering the medulla at the lateral edge of one and emerging at the lateral edge of the other. A hole was now made in the occipital bone and the cerebellum was removed. The free ends of the ligatures were next brought about the respective sides of the medulla and over the 4th ventricle. A knot was now tied in these. The result was a practically complete separation of the medulla from the pons with the exception of the pyramids. Microscopic examination, after disposal of the animal, showed, on the right

side, all of the medulla to be cut through excepting the right pyramid and an adjacent portion of the trapezoid body and medial lemniscus in the midline. On the left, a small amount of tissue lateral to the pyramid (region of the spinothalamic tract) in addition to the trapezoid tissue had also escaped. The only element of hypertonia noticeable was a very slight resistance to passive flexion of the right forelimb and a somewhat more marked resistance in both hindlimbs, more especially of that of the right side. Stimulation of either cortex produced phasic movements. These were loose and tremorous and had a low threshold. Stimulation of the right cortex sometimes caused slow elevation of the tail which was then temporarily held in this position. The medial sides of both anterior sigmoid gyri were more easily excited than the lateral portions. It may be interesting to note that we were unable to induce any epileptic seizures in this animal despite the application of extremely high current densities to the cortex.

We may conclude then that there is no element which lies oral to the medulla which does not travel by way of the pyramids and which is necessary for the phasic factor in cortically induced movement. The corticopontal fibers are among the elements thus eliminated. It remains to be seen what factors within the pyramids themselves may be involved but before we cite the results obtained by pyramid section let us examine what forelimb movements are elicitable from the cerebral cortex and how these representative points are arranged. Many maps of the excitable cortex of the cat have been prepared and published. Most of these show very poor agreement. The cause of much of the disparity seen is probably to be sought in the different techniques employed during stimulation and in the difference in directing interest. A large number of diverse results may in fact be easily obtained from the anterior sigmoid gyrus, especially by specifically denervating extraneous muscle groups, but with regard to forelimb movements in the intact animal only there is an underlying fundamental pattern. This pattern may be expressed briefly by saying that flexion (caudal) of the humerus upon the scapulo-humeral joint is dominated by the posterior half of the anterior sigmoid gyrus, extension of this bone by the anterior half, extension of the forepaw by the cortex lateral to the cruciate sulcus, abduction of the limb by the lateral half of the posterior sigmoid while flexion and extension of the elbow lie between the scapulo-humeral and forepaw areas.

In the intact (neurologically), mature cat a very small unipolar electrode is necessary to bring out this pattern. We have usually employed a silver spring of 0.25 mm. diameter wire for the active electrode (held in place by a special attachment of the Horsley-Clarke instrument) and the frame of the Horsley-Clarke itself for the indifferent electrode. With a variable-frequency stimulator it is possible to get fine discriminating and tonic movements from the optimal portions of these representative points. If the electrode is placed at neutral, intermediate points (the regions which the older English experimenters formerly called "zones of confusion") phasic movements occur and if a unipolar ball (2 mm. diameter) or bipolar electrode is used nothing but phasic movements result if the cat is in good condition. If there is hemorrhage from the pial vessels, stasis of the superior longitudinal sinus, damage to the cerebral tissue, general "shock" or, if the cat is young, tonic movements are likely to be the only variety elicitable. (In the following

experiments the bipolar, wandering electrode was used on the cortex as usual.)

The pyramids were exposed by the ventral approach in one animal and a lesion of the ventral surface of the right pyramid was made with a small cautery tip. The cortices were exposed and stimulated. Stimulation of the left cortex gave phasic movements as usual but stimulation of the right produced tonic movements only. In this animal it appeared to us that there was a suggestion of dissociation between extensor and flexor movements in the tonic (left) leg. Two more animals were accordingly prepared in a similar manner and more attention was paid to the portion of the anterior sigmoid gyrus stimulated. Excitation of the lateral portion of the anterior sigmoid gyrus produced tonic flexion but tonic extension was obtained from the medial portion.

Ten animals were now prepared with unilateral subtotal pyramidal lesions of varying size and position, in the right pyramid, just below the pons. The ligature instead of cautery was used. No correlation between the physiologic result and position of these lesions could be established upon microscopic examination. It was, however, observed that very small lesions regardless of position were accompanied by the abolition of the phasic factor and the appearance of the dissociation of flexion and extension noted above. In the case of large lesions the medial portion of the gyrus was inexcitable and tonic extension could not be evoked but no matter how large the lesion was (nor apparently no matter how it was placed, *i.e.*, whether laterally or medially in the pyramid) tonic flexion could always be evoked if any pyramidal fibers were left intact. Thus a situation in which tonic extension alone could be produced was never obtained. Extirpation of the opposite cortex (from that being stimulated) and isolation of the motor cortex of the same side from its surrounding parietal tissue never affected the nature of the above results except insofar as they caused deterioration of the preparation.

That these effects are mediated by the pyramids and nothing else is strongly indicated by various results which have been reported above but it is a simple matter to prove conclusively that this is the case by complete section of one pyramid alone. If this is done carefully, stimulation of the opposite cortex gives perfect phasic movements while stimulation of the anterior sigmoid gyrus of the same side produces a generalized inhibition of movement. This experiment was performed on two cats. Inhibition by cortical stimulation following double pyramid section has already been reported by Tower and Hines (1935). Our results are in complete accord with their report and add the insignificant information obtained by cutting one pyramid alone and at a different level from the one they chose. Epileptic seizures could easily be induced in all animals of the above type by stimulating the cortex corresponding to the cut pyramid (opposite to it) whereas, it will be recalled, they could not be induced when only the pyramids connected the cortex with the cord.

None of the above animals in which the pyramids were traumatized exhibited any evidence of spasticity nor hypertonia in such spontaneous movements as they displayed in the few short hours during which they were kept. These movements moreover showed the usual phasic elements.

Discussion

The question now arises as to how partial section of the corticospinal tract can bring about the above noted conversion. From this and the earlier, report we have the following observations to consider: (i) deafferentation abolishes the phasic factor in cortically induced movement; (ii) so also does corticospinal tract damage; (iii) flexion and extension may be dissociated in the cortex by pyramid damage; (iv) extension can be completely eliminated by partial corticospinal section but flexion cannot; (v) discriminating cortical stimulation gives rise to fine tonic movements; (vi) a deteriorated or immature cortex responds tonically; (vii) a single muscle of the forelimb may be activated phasically by the cortex in spite of the fact that all other muscles of both forelimbs and the skin of the region are completely denervated.

Considering the first and second observations together it would seem

unreasonable to suppose that phasic movement depends upon alternate activation of the points of cortical representation of flexion and extension at the cortical level. On the contrary, both observations are in favor of a uniform steady outflow to both flexors and extensors which is somehow converted at the spinal level and by afferent impulses into an alternating discharge. That it is unnecessary to consider afferent impulses from opposing muscular action as a factor in this fundamental segmental arrangement is indicated by the seventh observation and that it is not simply the result of kinesthetic stimulation is indicated by the first two observations.

That the mechanism for phasic reaction is essentially a fundamental pattern of cord morphology would seem to be an inescapable conclusion. That isolated spinal cord segments are capable of rhythmic activity is, of course, a commonplace but it is also true that very forceful and rapid phasic activity may be produced by capsular stimulation after ablation of the cortex, by thalamic irradiation in animals from which the motor cortex has been out for months and by the bursts which occur in the "rage"-like reactions of chronic thalamic animals. Besides the second stage of epileptic seizures is clonic and although such seizures are believed to be of cortical origin the responsible impulses do not travel in the pyramids. Possibly the corticospinal system should be looked upon as a mechanism superimposed upon this fundamental pattern in such a fashion as to interdigitate with and supplement it without actually entering into its basic arrangement. That this relationship is complex and must to some extent reflect myologic arrangement is shown by the gross nature of the deformation of the functional pattern which is produced by interference with a portion of it. That the pattern is more easily deformed upon the extensor than flexor side (iv above) would seem to be, in some measure, a reflection of the greater functional value which the flexor system possesses in an animal such as the cat which depends for its defense and food upon the flexor movements of clawing, climbing and catching (with its paws). We may ask whether, by the term "greater functional value," we are to understand greater flexor strength, more extensive flexor innervation or both? Probably the two situations are mutually interdependent. At one period of the work we thought that the fibers dealing with extension might travel in the most lateral third of the pyramid whereas flexion was represented throughout it but we were not able to convince ourselves of the validity of this observation. Whether they are specifically localized or not, however, they seem to be far less numerous than the flexor fibers.

Observations five and six seem to be essentially related with two and three. Apparently when the motor area is widely activated either by a "broad" stimulus or by means of its own intracortical association mechanisms its normal response is a widespread, steady, intraspinal activation of the limb area involved. The intrinsic spinal mechanisms convert this into phasic activity. In cases in which there is a defect in this widespread pyramidal discharge (due to selective stimulation, death or immaturity of cortical neurons or interruption of their axons) the intraspinal mechanism is not

called into play. The nature of the defect which occurs, when only cortical dissociation appears, is difficult to determine since both flexion and extension are still separately elicitable but not fusible. There is, moreover, a change in the cortical pattern of the excitable points. We have not been able to come to any conclusion about the nature of this (the question is under further investigation) since our series of animals was not designed for that purpose but a shifting in the cortical pattern is also seen in cases in which all the muscles but one of a limb are denervated (the cortical area capable of exciting this muscle becoming progressively larger as other muscles are rendered non-functional.) Again in strychnine poisoning, as is well-known, the entire motor cortex may become an extensor representation. All these observations tend to render the old statement that "not muscles but movements are represented in the cortex" about as meaningless as could be imaggined and add to the difficulty in comprehending how the suprasegmental pattern is superimposed upon the fundamental, spinal, phasic mechanism. Whether or not this phasic mechanism will be activated seems to be determined then by two factors, first the activity of a large number of corticospinal fibers and second by the integrity of the intrinsic spinal mechanism. Thus the incoming kinesthetic impulses from a contracting muscle are not enough to produce phasic movement as we know from extrapyramidal stimulation. They must encounter a certain spinal, balanced discharge-reserve, one of the means of the establishment of which is relatively full pyramidal activity. The kinesthetic impulses may therefore be looked upon as tipping this balance of discharge-reserve now in one direction and now in another.

It is interesting to compare the effects of extrapyramidal stimulation with those obtained from corticospinal activation. In the former case a phasic discharge is rare (Mettler, 1940) and one wonders if it would not be useful to look upon any given extrapyramidal system as a partial motor unit. If two oppositional extrapyramidal units are simultaneously activated, just out of phase with each other, rather clumsy, phasic movements can be produced such as swinging of the head from side to side or a curious, serpentine wriggling of the spinal column. One of the difficulties in the attempt to produce nice, discriminating, phasic movements of this type is that most extrapyramidal units respond slowly and build up to a maximum which again breaks down slowly. Even in self-originated, extrapyramidal movements this is seen. Thus the decorticated dog, as previously reported (Mettler, Mettler and Culler, 1935), has considerable difficulty in starting and stopping movements. The sudden origination of an "upper level" movement is certainly a function of the pyramidal tract but we have no evidence that inhibition follows this course. Since inhibition is the subject of another communication we may dispense with its discussion for the present.

The functional importance of adequate sensory activity in determining the character of motor responses can hardly be overemphasized. Not only is good sensory activity important at both the cortical and spinal levels in pyramidal function but it also enters into the manifestations of extrapyram-

idal activity as well. Thus in the course of recent experiments with bulbocapnin we observed that deafferentation of the forelimb abolishes any evidence of the action of the drug in the extremity concerned.[2] Again deafferentation is not without an effect even in such an impelling condition as strychnine poisoning.

The fact that movements and particularly phasic movements are possible in the deafferented animal might be superficially supposed to remove from the realm of clinical significance such phenomena. Still the experienced neurosurgeon knows that patients will not use a limb so affected if the involvement is extensive and that in all cases it produces, to some degree, an effect which amounts, for practical purposes, to paralysis. The phasic movements seen in the usually flail-like deafferented extremities of our cats were not of a pyramidal type and, in fact, it was pyramidal function which was most seriously affected. Although such animals would finally succeed in removing, with the anesthetic limb, an empty can placed over their heads the movements were predominantly of the diffuse spinal type seen in the sort of struggling the decorticated animal exhibits. In such cases a tonic, dyskinesic element previously undetected would crop out in overflexion and extensor thrusts which but for a temporary hypertonia were suspicuously choreiform. In itself this seems relatively unimportant. The important point is that in the clinic a neural dysfunction is not ordinarily seen, as it may be revealed in the laboratory. What is seen is the subject's reaction to the basic dysfunction which is often effectively hidden away under a rather bizarre syndrome. The distinction between original dysfunction and compensation for this should always be attempted in spite of the difficulties involved.

Conclusions

1. The conversion of a cortically induced phasic movement into a tonic movement by dorsal root section is a true neural effect and is not related with (a) acute conditions, (b) the route by which the dorsal roots are approached nor (c) vascular damage.

2. The conversion of a cortically induced phasic movement into a tonic movement by lesions placed in the "position of the ventral spinocerebellar tract" as previously reported is the result of partial damage to the pyramidal system and phasic activity is not converted into that of a tonic type by (a) damage done to the spinocerebellar tract nor (b) rubrospinal tract elimination.

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[2] Stimulation of the cortex of an animal given bulbocapnin, 40 mgm. per kg. subcut., sometimes gives tonic flexion but more usually phasic movements of a tremorous nature are obtained. Epileptic seizures are easy to evoke. Deafferentiation of the forelimbs of such animals totally abolishes (in that region) the plastic tonus, which is characteristic of bulbocapnin poisoning. Such deafferented limbs do not respond to vestibular activation nor do they display any tendency to cling to objects. Stimulation of the cortex of deafferented, bulbocapnin-poisoned cats sometimes gives tonic flexion but more frequently loose, flabby jerks of the flexor muscles alone is all that is obtained.

3. Cortically induced phasic movements furthermore cannot be converted into tonic movements by (a) removal of all nor any part of the cerebellum nor (b) destruction of the cerebellar nuclei.

4. Cortically induced phasic movements may be obtained even though only the pyramids remain in connection between the medulla and cortex (though the medulla be entirely transected excepting for the pyramids).

5. Epileptiform seizures cannot be evoked from the cortex if only the pyramids are intact but can be evoked if they alone are severed. Further the cortex of one hemisphere still retains its capacity for spinal inhibition after its corresponding pyramid has been severed.

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FOREBRAIN AND RAGE REACTIONS

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INTRODUCTION

NEARLY a half a century has passed since Goltz (1892) in his classic account of a decorticate dog described the onset of abnormal emotional hyperexcitability, the animal being provoked to a marked reaction of anger and rage even by slight and innocuous stimuli. These observations were confirmed by the majority of later investigators, Rothmann (1923) on a decorticate dog, Dusser de Barenne (1920) and Bard and Rioch (1937) on decorticate cats, while negative results were reported only occasionally (Mettler and Culler, 1935). No one has ascertained, however, what part of the forebrain must be eliminated to cause the phenomenon. Whereas Goltz (1884) observed it after ablation of the frontal lobes and anterior sigmoid gyri, a number of observers (Barris, 1937, Magoun and Ranson, 1938) did not obtain these reactions even after extensive lesions of the frontal lobes. The experiments of Cannon and Britton (1935), Bard (1928), Bard and Rioch (1937) indicated that these fits of rage are due to the release of subcortical ganglia from cortical inhibition, particularly a release of the posterior hypothalamus as far as the vegetative component of these reactions is concerned, the somatic component probably having its center in the mesencephalic tegmentum and its continuation into the hypothalamus (Hinsey, Ranson and McNattin, 1930.)

A systematic study of the problem of rage reactions, therefore, must deal with all those parts of the forebrain which send efferent impulses to the hypothalamus and the midbrain tegmentum respectively. The following systems require consideration.

1. *Frontal lobe.* The precentral region and area frontalis agranularis respectively receive impulses from and send fibers (Fig. 1, 1a) to the anterior nucleus of the thalamus (Gruenthal, 1939). The Vicq d'Azyr bundle seems to contain not only fibers from the mammillary body to the anterior nucleus, but also fibers of conduction in the opposite direction (LeGros Clark, 1932). Impulses from the anterior nucleus may reach the hypothalamus also by way of the strio-pallidum, since degenerations from the anterior nucleus to the caudate nucleus have been observed (E. Sachs, 1909). In monkeys degenerating fibers (Fig. 1, 1b) have been traced from the precentral gyrus to the septohypothalamic nuclei and to the periventricular region (Mettler, 1935). After injury to the white matter of the frontal pole in a guinea pig Wallenberg (1934) traced a tractus neocortico-septalis (Fig. 1, 1c) to the dorsofrontal part of the septum pellucidum. The septal nuclei send a septohypothalamic tract joining the medial forebrain bundle to the hypothalamus (Loo, 1931). Also in experiments in monkeys Mettler (1935) found that

prefrontal lesions gave rise to degeneration of fibers that could be traced to the septum. Mettler (1935) also traced in the monkey fibers from area 9 of the frontal pole into the corpus striatum and the subthalamus. According to this author, the medial nucleus of the thalamus receives fibers from the region anterior to the precentral gyrus. The medial nucleus of the thalamus may be connected with the hypothalamus by periventricular fibers.

2. *Parietal lobe.* Cortico-subthalamic fibers (Fig. 1, 2) arise, according to Mettler's (1935) experiments in monkeys, from the anterior and posterior

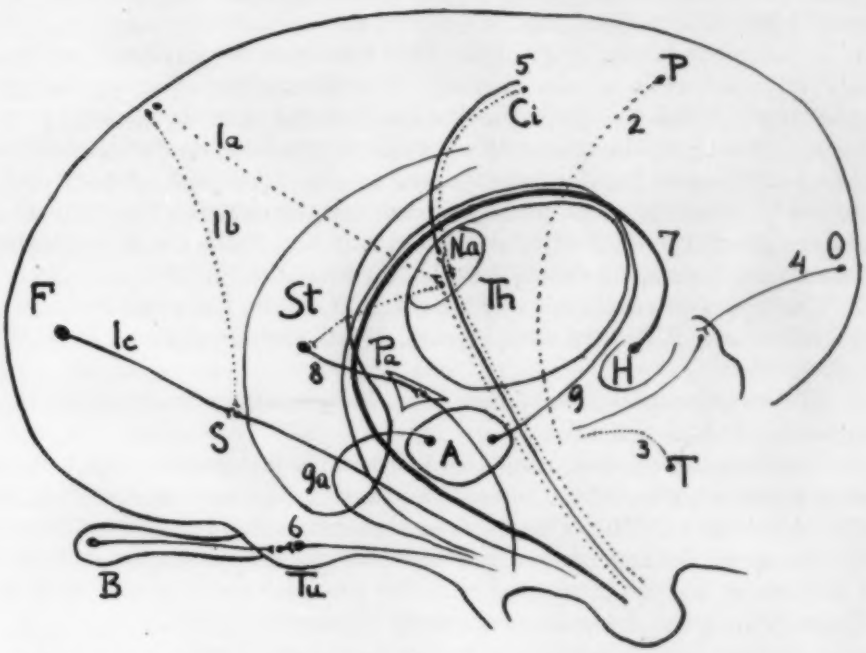

FIG. 1. Corticofugal systems to the hypothalamus and subthalamus. A, Amygdala; B, Olfactory bulb; Ci, Gyrus cinguli; F, Frontal lobe; H, Hippocampus; Na, anterior nucleus; O, Occipital lobe; P, Parietal lobe; Pa, Pallidum; S, Septum; St, Striatum; T, Temporal lobe; Th, Thalamus; Tu, Olfactory tubercle. (For further details see text.)

marginal gyri and probably also from the medial parietal cortex. Probst (1903) traced degenerating fibers from the parietal lobe to the anterior nucleus of the thalamus in dogs and cats; the regio centralis, however, did not escape injury.

3. *Temporal lobe.* Degenerating fibers were followed from the lateral surface to the temporal lobe (Fig. 1, 3) to the subthalamus and to the lateral hypothalamic nuclei (Mettler, 1935). From the anterior end of the occipitotemporal gyrus and from the upper end of the superior and middle temporal gyrus, cortico-subthalamic fibers seem to originate (Mettler, 1935).

4. *Occipital lobe.* Centrifugal fibers from the occipital lobe end in the tectum of the superior colliculi (Fig. 1, 4). From here a system arises that

could be followed into the subthalamus (Forel's field H_1, H_2) and zona incerta, Godlowski (1936).

5. *Gyrus cinguli.* Although the connection between the corpus mammillare and the anterior nucleus of the thalamus and the gyrus cinguli is mainly cortico-petal (Papez, 1939), the possibility of the existence of inhibitory influences from the gyrus cinguli through the anterior medial thalamic nuclei to the hypothalamus (Fig. 1, 5) has to be considered (Grinker, 1939). Fibers of the fornix longus perforating the corpus callosum may also represent a connection between medial parts of the cerebral cortex and the base of the diencephalon (Obersteiner, 1912).

6. *Olfactory tubercle.* (Fig. 1, 6) This structure sends impulses to the closely adjacent cells of the dorsally situated motor olfactory striatum (Papez, 1929) which lie ventral to the head of the caudate nucleus proper. Fibers originating in the motor olfactory striatum join the medial forebrain bundle and descend to the hypothalamus (olfactory peduncular tract of Papez). Also fibers from the pyriform lobe join this bundle. Fibers from the secondary olfactory centers in the pallium may also reach the hypothalamus by way of the lateral forebrain bundle (Kuhlenbeck, 1927).

7. The *hippocampus-fornix* system (Fig. 1, 7) to the mammillary body and to the tuber is well defined (see Ingram, 1940) and requires no further description.

8. The *striatum-pallidum* system (Fig. 1, 8) is continued by pallidofugal fibers which end in the tuber.

9. The *amygdaloid nuclei* give rise to the stria terminalis (Fig. 1, 9), the fibers of which are distributed to most major hypothalamic nuclei (Kappers, Huber and Crosby, 1936). There exist in addition (Fig. 1, 9a) fibers from the lateral group of the amygdaloid nuclei which have no connection with the stria terminalis but are connected with the preoptic and hypothalamic area by fibers joining the anterior commissure (Humphrey, 1936).

MATERIAL AND METHODS

The results reported in this paper are based on observations on the spontaneous general behavior and emotional excitability of 66 cats in which the various systems described above were eliminated in acute experiments; twelve dogs were used in which extirpation of the frontal lobes, of the lateral surface of the parietal and temporal lobes had been performed for other purposes, the animals having survived for from four weeks to over one year.

The cats were operated under ether anesthesia and the dogs under nembutal anesthesia. In the experiments in which large parts of the hemispheres were removed (*e.g.*, lobectomies performed) ligature of the carotid arteries preceded the brain operation. Lesions of the subcortical ganglia or tracts were usually made by electrolysis with the aid of Horsley-Clarke's stereotaxic apparatus. In a few cases the ablations were performed in two stages, in order to ascertain whether one sided elimination of the systems under study was sufficient. Since these unilateral operations gave inconclusive results, in the majority of the experiments bilateral lesions were placed in a one stage operation.

RESULTS

In the acute experiments on cats, the animals in which positive results were obtained, *i.e.*, "rage positive" animals, exhibited an abnormally in-

creased motor activity. This appeared in some animals immediately upon awakening from the ether anesthesia, in others after a latent period covering a few up to 45 min. Restlessness was especially apparent when liberty of movement was restricted, *e.g.*, by keeping the animal in a small cage. Thus confined, it would go through recurrent fits of violent activity at intervals of five to fifteen minutes. Often it pushed against the wall or corner of the cage. Frequently it was seen struggling with its forepaws or trying to jump against the lid of the cage. These movements were accompanied in typical cases by clawing, waving of the tail, hissing or biting. The abnormal excitability was promptly apparent if one tried to remove the animal from its cage or to raise it by the back of the neck. The animal would hiss, sometimes try to bite and claw or jump into the air.

When such animals were left in the room without restraint the fits were less marked. They exhibited, however, a tendency to run about rather aimlessly, to press head-on against any resistance they encountered, and to withdraw into corners. Sometimes the cats would jump almost vertically upward.

Polypnea was striking and observed often directly after operation even before recovery from ether anesthesia. The increased respiratory rate, up to 150 per min., sometimes greater, often became especially prominent during the fits of motor excitement, and often outlasted the motor component of the fit. The exhausted animal would fall into a recumbent position, the polypnoea continuing. The picture of the motor component of the rage reactions as here described is not always developed in all its elements. We considered, however, an experiment as rage positive only if several of the above described symptoms appeared combined; the appearance of a single component, *e.g.*, restlessness, did not seem to justify the diagnosis of rage reaction.

It should be emphasized that whereas these motor outbursts were often accompanied by signs of hyperactivity of the vegetative nervous system, *e.g.*, pupillary dilatation, piloerection, often there occurred a dissociation of motor and vegetative manifestations. For example, as nearly as we could judge by simple observation, there were occasions when no evidence of vegetative discharge seemed to accompany the motor outbursts and polypnea. It is, of course, possible that recording devices might have captured vegetative disturbances like vasoconstriction which escaped our powers of gross observation.

As to chronic symptoms, witnessed in dogs, they were similar to those described by Goltz (1892): overexcitability, barking, baring of the teeth, attempts to bite, etc. if one approached the animal or tried to lift it from the cage.

Experimental elimination of the following regions failed to produce outbursts of rage reactions: sigmoid and coronal gyri, lateral surface of the parietal lobe and the gyrus marginalis on its medial surface, lateral surface of the temporal lobe, lateral as well as medial surface of the occipital lobe.

The frontal poles (frontal lobes in front of the sigmoid gyri) were destroyed in eight cases, either alone or in combination with the motor cortex, with the medial surface of the frontal lobe, with the gyrus rectus and with the tip of the head of the caudate nucleus respectively. Definite outbursts of rage failed to appear in seven of these eight cases; five of them showed a more or less marked hypermotility as was previously observed by Magoun and Ranson (1938) and Langworthy and Richter (1939). This hypermotility by itself did not seem to warrant the inference that we were dealing with rage reactions. In one animal there were definite outbursts of rage. In this case the lesion encroached not only upon the head of the striatum but also upon the white matter dorsal to the olfactory tubercle so that the change in behavior could hardly be ascribed to the frontal pole lesion alone. This inference received further support from three subsequent experiments in which positive reactions were obtained. In these three animals the frontal lobectomy was performed in such a manner that the level of the dorsal entry of the section (ansate sulcus) corresponded with that of the preceding experiments. The ventral end of the section on the base, however, instead of being anterior to the olfactory tubercle, lay on the anterior border or a few millimeters in front of the optic chiasma.

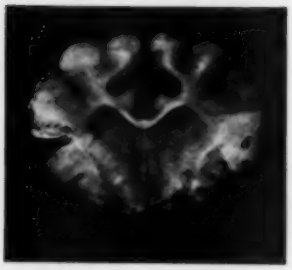

FIG. 2. Cat 66. Bilateral lesion of the olfactory tubercles. 5/24/40 11:00 A.M.–12:10 P.M. Ether anesthesia. Ligature of both carotid arteries. Cauterization of both olfactory tubercles on the overhanging brain. 12:50–4:00 P.M. Repeated spontaneous outbursts of hypermotility, pushing against corners of cage, struggling. Respiratory rate up to 60 per minute. Excitement and struggling are increased if one takes the animal from the cage and holds it by the back of the neck.

In these animals with bilateral frontal lobectomy in which expressions of rage appeared, a peculiar association with cataleptic reactions could be observed. After stopping their running movements or struggling, the animals sometimes assumed peculiar postures for several minutes. This cataleptic reaction resembled that described by Barris following the bilateral removal of the rostral part of the neocortex in cats, the animals showing no rage reactions.*

These experiments directed our attention to the base of the brain, particularly to the olfactory centers. Using Karplus and Kreidl's method of operation on the overhanging brain the olfactory bulbs were destroyed on both sides by thermocautery, or their stalks were sectioned. While these operations produced no or only slight and transitory effects, lesions encroaching upon the olfactory tubercles or isolated lesions of the tubercles (Fig. 2) were followed by distinct rage reactions (6 cases), particularly if the lesion extended medialward to the septum pellucidum.

* The appearance of such cataleptic symptoms, however, seems not specifically related to the frontal lobes. Occasionally it could also be found in animals with other lesions, *e.g.*, bilateral injury to the amygdaloid nuclei.

Lesions of the hippocampus-fornix system were produced by electrolysis with the help of the Horsley-Clarke apparatus (Fig. 3); or the corpus callosum was exposed and incised, and the lesions were placed in the hippocampus by electrocautery, or the fornices were cut before they descended into the thalamus. Of seventeen cases in which acute lesions of this system were made, four did not show manifestations of rage (#45$_1$ unilateral lesion of the hippocampus, #44 puncture of the fornices, #43 and #47$_1$ puncture of the commissura hippocampi). In three cases (#6, 34, 54) there was a certain restlessness, but without definite rage reactions. Ten experiments could be considered rage positive showing either the full developed picture of rage or at least rudimentary reactions (*e.g.*, vocal expressions of rage). In three of these ten cases the lesion encroached upon the most dorsal part of the thalamus (#16, 17) and the stria medullaris (#40), respectively, in four others upon the Septum pellucidum immediately in front of the fornices (#41, 42, 45, 55). To this latter group belong animals (#41, 55) with very marked rage reactions.

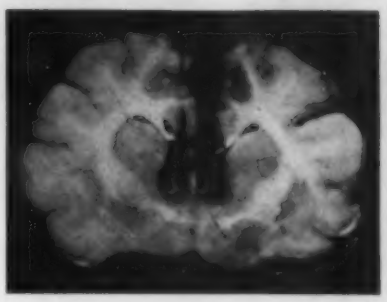

FIG. 3. Cat 41. Electrolytic lesion of the fornices and the septum pellucidum. 2/7/40 10:45–11:50 A.M. Electrolytic lesion under ether anesthesia. 12:00–4:30 P.M. Very marked restlessness and excitement. Hissing, clawing and jumping against the lid of the cage; tries to bite when approached. Respiratory rate up to 120 per minute.

Since a longitudinal section of the corpus callosum had to be performed in order to expose the hippocampus, and since a part of the callosal fibers and of the gyrus cinguli had to be punctured in placing the electrolytic lesions, control experiments with lesions of these parts were necessary. Median section of the corpus callosum and also puncture of the gyrus cinguli with the needle of the Horsley-Clarke apparatus failed to produce rage reactions. In seven cats extensive lesions of the gyrus cinguli were performed by electrocautery. Four of these experiments were rage negative. In one case (#35) in which definite outbursts of rage appeared, there was a slight additional injury to the hippocampus; in a second animal (#37) showing rage a small cotton sponge had been left inadevertently in the operative cavity apparently pressing upon the underlying corpus callosum and hippocampus. Finally, in one cat (#20) in which bilateral frontal lobectomy had failed to produce changes in emotional behavior, additional extirpation of the gyri cinguli was followed by transient and weak outbursts of rage. The lesion in this animal reached deeply into the white matter close to the head of the caudate nucleus. Thus, the influence of the gyrus cinguli upon the subcortical mechanisms responsible for manifestations of rage is hardly very pronounced, while an influence of the hippocampus-fornix system is more definite. It should, however, be admitted that rage symptoms may be enhanced, if the lesion of the fornices

is combined with a lesion of centrifugal fibers from the gyrus cinguli. This is suggested by the observation that the outbursts of rage were particularly pronounced in cases in which the lesion of the fornices encroached upon the septum pellucidum, which contains fibers of the fornix longus from the gyrus cinguli to the base of the brain. A concomitant lesion of the neocortico-septal tract may, however, also play a part in these cases, *e.g.*, as far as the production of the hypermotility is concerned, since ablation of the frontal poles may cause a certain restlessness (see above).

FIG. 4. Cat 48. Bilateral electrolytic lesion of the amygdaloid nuclei 2/27/40 11:30–12:30 P.M. Electrolytic lesion under ether anesthesia. 12:40–3:50. Nearly continuous hypermotility, tendency to circus movements (clockwise), pushing against the walls and corners of the cage, jumping against the lid and clawing, struggling, howling. The outbursts of excitement are often followed by catatonic postures.

After bilateral electrolytic lesions had been produced in the head of the caudate nucleus (sparing the motor olfactory striatum), the emotional excitability of the cats was not increased. The same result held true for bilateral lesions which extended to the tail of the caudate nucleus. Definite outbursts of rage reactions appeared after bilateral electrolytic lesions of the oral part of the amygdaloid nuclei (Fig. 4). Control experiments showed that the animals remained quiet after punctures at the same coordinates of the Horsley-Clarke apparatus provided the lesions remained dorsal to the amygdaloid nuclei. In view of the positive results from amygdaloid lesions one would presuppose that bilateral section of the stria terminalis would give similar results. Such, however, was not the case. This failure is probably due to the fact that the stria terminalis is not the sole efferent pathway of the amygdaloid ganglia, as pointed out in the introductory anatomical remarks. The possibility must of course be borne in mind that the lesions of the amygdaloid nuclei also affected efferent fibers of the pyriform lobe. Lesions of the pyriform lobes produced by thermocautery on the overhanging brain, however, evoked only slight and transient symptoms of rage as long as they remained superficial.

COMMENT

The fact that injury of the olfactory tubercles is followed by rage reactions may explain why some authors observed such reactions after extirpation of the frontal lobes (Goltz, 1884) while other authors who removed

neocortical parts only (Barris, 1937; Magoun and Ranson, 1938; Bard, 1939) failed to elicit such changes of behavior. The appearance of these phenomena after incision at the base of the brain a few millimeters in front of the optic chiasma (Fulton and Ingraham, 1929) seems to be due mainly to section of the descending fibers from the olfactory tubercles (perhaps also fibers from the septal nuclei and fibers from the amygdaloid complex that first enter the anterior commissure and thence pass caudalward).

The experiments presented in this communication indicate that rage reactions appear with lesions of the olfactory tubercles, of the amygdaloid nuclei and to some extent also with lesions of the hippocampus-fornix system. These parts of the forebrain, all phylogenetically old, enter into the formation of the central olfactory system. The appearance of these reactions, however, cannot be explained simply on the basis of elimination of afferent olfactory impulses as shown by a comparison with the effects of extirpation of the olfactory bulbs. In this connection it is pertinent to recall that not only the olfactory tubercle and the amygdaloid complex (Edinger, 1911; Spiegel, 1919) but also the hippocampus (LeGros Clark, 1932) are rather well developed in micro- and anosmatic mammals. This had raised the thought that these structures may also subserve non-olfactory functions (Edinger, 1911; Herrick, 1933; Papez, 1937).

In connection with our problem the views of Herrick (1933) and Papez (1937) possess a special interest. The former assumes the existence of activating impulses from the olfactory cortex upon the cerebrum, influencing affective tone. According to the concept of Papez, hippocampo-fugal impulses acting upon the mammillary bodies and thence upon the gyrus cinguli play an important role in the mechanisms of emotive processes. This in turn provokes the question whether the changes in behavior following decortication are only symptoms of release due to the loss of cortical inhibition or whether stimulation of excitatory systems also plays a part.

It is well known that the cortex may send stimulating, as well as depressing impulses, to a certain system such as the vasomotors, for instance. The occurrence of rage symptoms for several months after decortication or after prechiasmal punctures (Fulton and Ingraham, 1929) shows, of course, that following these procedures a certain overexcitability of subcortical mechanisms responsible for bodily manifestations of rage may develop as a result of the loss of inhibitory impulses or as an isolation phenomenon. This does not exclude the possibility, however, that corticofugal systems may exist which have an excitatory or facilitating influence upon the subcortical apparatus innervating rage reactions and that stimulation of such corticofugal systems may contribute to the genesis of the manifestation of rage in the acute preparation.

On stimulation of the rostral pyriform area Rioch and Brenner (1938) observed struggling and biting. By stimulation of the subfornical component of the medial forebrain bundle Ranson and Magoun (1933) elicited motions of spitting, while stimulation of the preoptic region, the medial forebrain

bundle or of the fornix in the rostral part of the hypothalamus failed to produce respiratory acceleration, running movements or dilatation of the pupils, reactions which are observed upon hypothalamic stimulation. Yet the existence of excitatory or facilitating corticofugal impulses from the hippocampus is suggested by the experiments of Klüver and Bucy (1939). In accordance with the theory of Papez, ablation of the temporal lobes with destruction of the hippocampi was followed in their chronic experiments* by a diminution of reactions of fear and anger and only with regard to sexual reactions was the emotional activity increased. Thus, it seems not improbable that stimulation of corticofugal fibers has its place in the genesis of the rage reactions in the acute preparation.

It will hardly be surprising to find differences in the effect of forebrain lesions in carnivores on the one hand and in monkeys and men on the other. The cortical representation of the mechanisms of emotional expression may assume a greater significance as one ascends the phylogenetic scale (Fulton, 1939). Furthermore a comparison with observations on monkeys after lesions of the frontal lobes (Jacobsen, 1931; Kennard and Ectors, 1938; Richter and Hines, 1938) and with clinical experiences (Davison and Kelman, 1939) with forced laughing and crying associated with lesions of the neocortex suggests the possibility that with progressive encephalization parts of the neocortex develop an inhibitory influence upon the subcortical mechanisms responsible for affective reactions. Such an influence is exerted in the more primitive brain of carnivores chiefly by phylogenetically old parts of the forebrain.

Summary

A study was made of the parts of the forebrain which are related to the initiation of rage reactions observed in decorticate cats and dogs. Lesions restricted to neocortical areas failed to produce rage reactions. Following lesions of the frontal poles hypermotility could be observed but no convincing outbursts of rage. Definite manifestations of rage appeared if the lesions (*e.g.*, extirpation of the frontal lobes) encroached upon the olfactory tubercles or followed isolated lesions of the tubercles, whereas destruction of the olfactory bulbs or section of their stalks had no or only slight effects. After acute lesions of the hippocampus-fornix system rudimentary, or in some animals marked, rage reactions appeared, particularly in cases in which the lesion of the fornices encroached upon the septum pellucidum. Definite outbursts of rage were observed after bilateral lesions of the amygdaloid nuclei. Lesions of the pyriform lobes, as long as they remained superficial, evoked only slight and transitory symptoms of rage.

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* Klüver & Bucy operated upon their monkeys under sodium pentobarbital anesthesia, so that the animals slept immediately following the operation, while our acute experiments on cats were performed under ether anesthesia so that the acute stage following the operation could be observed as in Bard's acute experiments.

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